UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 6-K

REPORT OF FOREIGN PRIVATE ISSUER
PURSUANT TO RULE 13a-16 OR 15d-16
OF THE SECURITIES EXCHANGE ACT OF 1934

For the Month of July, 2016

Commission File Number: 001-35892

GW PHARMACEUTICALS PLC
(Translation of registrant's name into English)

Sovereign House
Vision Park
Histon
Cambridge CB24 9BZ
United Kingdom
(Address of principal executive offices)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F:

Form 20-F ☑  Form 40-F ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1):

Yes ☑  No ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7):

Yes ☐  No ☐
Other Events

On July 12, 2016, GW Pharmaceuticals plc (the “Company”) filed with the Securities and Exchange Commission (the “SEC”) a preliminary prospectus supplement pursuant to Rule 424(b)(5) under the Securities Act of 1933, as amended (the “Preliminary Prospectus Supplement”), relating to a proposed public offering of the Company’s American Depositary Shares (the “Public Offering”). The Preliminary Prospectus Supplement for the Public Offering contains updated company risk factor disclosure as well as an updated description of certain aspects of the Company’s business. Accordingly, the Company is filing information for the purpose of supplementing and updating the risk factor disclosure contained in the Company’s prior public filings, including those discussed under the heading “Item 3D. Risk Factors” in the Company’s Annual Report on Form 20-F for the year ended September 30, 2015, filed with the SEC on December 7, 2015 (the “20-F”). The Company is also updating certain aspects of the description of its business from that described under the heading, “Item 4B. Business” in the 20-F. The updated disclosures are filed herewith as Exhibit 99.1 and are incorporated herein by reference.

On July 12, 2016, the Company issued a press release related to the Public Offering. The press release is attached as Exhibit 99.2 and is incorporated by reference herein.

Exhibits

99.1 Updated Company Disclosure
99.2 Press Release dated July 12, 2016
SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

GW Pharmaceuticals plc

By: /s/ Adam George
   Name: Adam George
   Title: Chief Financial Officer

Date: July 12, 2016
As used in this Current Report on Form 6-K (“Current Report”), “GW Pharma,” the “Group,” the “Company,” “we,” “us” and “our” refer to GW Pharmaceuticals plc and its consolidated subsidiaries, except where the context otherwise requires. Epidiolex®, Sativex®, the GW logo and other trademarks or service marks of GW Pharma appearing in this Current Report are the property of GW Pharma. Trade names, trademarks and service marks of other companies appearing in this Current Report or the accompanying prospectus are the property of their respective owners.

FORWARD-LOOKING STATEMENTS

This Current Report on Form 6-K, contains forward-looking statements that are based on our current expectations, assumptions, estimates and projections about us and our industry. All statements other than statements of historical fact in this Current Report are forward-looking statements.

These forward-looking statements are subject to known and unknown risks, uncertainties, assumptions and other factors that could cause our actual results of operations, financial condition, liquidity, performance, prospects, opportunities, achievements or industry results, as well as those of the markets we serve or intend to serve, to differ materially from those expressed in, or suggested by, these forward-looking statements. These forward-looking statements are based on assumptions regarding our present and future business strategies and the environment in which we expect to operate in the future. Important factors that could cause those differences include, but are not limited to:

• the inherent uncertainty of product development;
• manufacturing and commercialization;
• our ability to submit and maintain INDs and NDAs with the FDA, including our planned submission of our NDA for Epidiolex in the first half of 2017;
• our ability to successfully design, commence and complete clinical trials;
• patents, including, but not limited to, oppositions and legal challenges;
• government regulation and approval, including, but not limited to, the expected timing of potential regulatory approval dates for Epidiolex;
• future revenue being lower than expected;
• the level of pricing and reimbursement for our products and product candidates, if approved;
• increasing competitive pressures in our industry;
• general economic conditions or conditions affecting demand for the products offered by us in the markets in which we operate, both domestically and internationally, being less favorable than expected;
• currency fluctuations and hedging risks;
• worldwide economic and business conditions and conditions in the industry in which we operate;
• our relationships with our customers and suppliers;
• increased competition from other companies in the industry in which we operate;
• changing technology;
• claims for personal injury or death arising from the use of products and product candidates produced by us;
• the occurrence of accidents or other interruptions to our production processes;
• changes in our business strategy or development plans, and our expected level of capital expenses;
• our ability to attract and retain qualified personnel, including with respect to our preparation for potential commercialization of Epidiolex;
• regulatory, environmental, legislative and judicial developments;
• our intention not to pay dividends; and
• factors that are not known to us at this time.

Additional factors that could cause actual results, financial condition, liquidity, performance, prospects, opportunities, achievements or industry results to differ materially include, but are not limited to, those discussed under “Risk Factors” or elsewhere in this Current Report, the accompanying prospectus and the documents incorporated by reference herein and therein. Additional risks that we may currently deem immaterial or that are not presently known to us could also cause the forward-looking events discussed in this Current Report and the accompanying prospectus not to occur. The words “believe,” “may,” “will,” “estimate,” “continue,” “anticipate,” “intend,” “expect” and similar words are intended to identify estimates and forward-looking statements. Estimates and forward-looking statements speak only at the date they were made, and we undertake no obligation to update or to review any estimate and/or forward-looking statement because of new information, future events or other factors. Estimates and forward-looking statements involve risks and uncertainties and are not guarantees of future performance. Our future results may differ materially from those expressed in these estimates and forward-looking statements. In light of the risks and uncertainties described above, the estimates and forward-looking statements discussed in this Current Report and the accompanying prospectus might not occur and our future results and our performance may differ materially from those expressed in these forward-looking statements due to, inclusive of, but not limited to, the factors mentioned above. Because of these uncertainties, you should not make any investment decision based on these estimates and forward-looking statements.

NOTE REGARDING EXPANDED ACCESS STUDIES

The expanded access studies we are currently supporting are uncontrolled, carried out by individual physician investigators independent from us, and not always conducted in strict compliance with Good Clinical Practices, all of which can lead to an observed treatment effect that may differ from one seen in placebo-controlled trials. Data from these studies provide only anecdotal evidence of efficacy for regulatory review, although they may provide supportive safety information for regulatory review. These studies contain no control or comparator group for reference and are not designed to be aggregated or reported as study results. Moreover, data from such small numbers of patients may be highly variable. Such information, including the statistical principles that the independent investigators have chosen to apply to the data, may not reliably predict results achieved after systematic evaluation of the efficacy in company-sponsored clinical trials or evaluated via other statistical principles that may be applied in these trials. Reliance on such information may lead to Phase 2 and/or Phase 3 clinical trials that are not adequately designed to demonstrate efficacy and could delay or prevent our ability to seek approval of Epidiolex. Physicians conducting these studies may use Epidiolex in a manner inconsistent with GW’s protocols, including in children with conditions different from those being studied in GW-sponsored trials. Any adverse events or reactions experienced by subjects in the expanded access program may be attributed to Epidiolex and may limit our ability to obtain regulatory approval with labeling that we consider desirable, or at all.
COMPANY OVERVIEW

We are a biopharmaceutical company focused on discovering, developing and commercializing novel therapeutics from our proprietary cannabinoid product platform in a broad range of disease areas. In our 18 years of operations, we have established a world leading position in the development of plant-derived cannabinoid therapeutics through our proven drug discovery and development processes, our intellectual property portfolio and our regulatory and manufacturing expertise. Our lead cannabinoid product candidate is Epidiolex, a liquid formulation of pure plant-derived cannabidiol, or CBD, for which we retain global commercial rights, and which is in development for a number of rare childhood-onset epilepsy disorders. We received Orphan Drug Designation from the U.S. Food and Drug Administration, or FDA, for Epidiolex for the treatment of Dravet syndrome, Lennox-Gastaut syndrome, or LGS, Tuberous Sclerosis Complex, or TSC, and Infantile Spasms, or IS, each of which are severe infantile-onset, drug-resistant epilepsy syndromes. Additionally, we have received Fast Track Designation from the FDA and Orphan Designation from the European Medicines Agency, or EMA, for Epidiolex for the treatment of Dravet syndrome. In March 2016, we reported positive results from the first pivotal Phase 3 trial of Epidiolex in Dravet syndrome. In June 2016, we reported positive results from the first pivotal Phase 3 trial of Epidiolex in LGS. We expect to submit a New Drug Application, or NDA, to the FDA in the first half of 2017 for Epidiolex in both Dravet syndrome and LGS. We are also building an experienced commercial team in the United States in preparation for the potential future launch of Epidiolex.

We have a deep pipeline of additional cannabinoid product candidates with an increasing focus on orphan pediatric neurologic conditions. Our pipeline includes cannabidiivarin, or CBDV, which is in Phase 2 development in the field of epilepsy and is also being researched within the field of autism spectrum disorders, or ASD. In addition, we have received Orphan Drug Designation and Fast Track Designation from the FDA for intravenous CBD for the treatment of Neonatal Hypoxic Ischemic Encephalopathy, or NHIE, which is expected to enter Phase 1 development in the fourth quarter of 2016.

Our Product and Product Candidates

GW Product Pipeline Summary

Epilepsy and Pediatric Neurology

<table>
<thead>
<tr>
<th>Product/Product Candidates</th>
<th>Indication</th>
<th>Partner(s)</th>
<th>Status</th>
<th>Expected Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidiolex (CBD)</td>
<td>Childhood-onset epilepsy</td>
<td>We retain global rights.</td>
<td>Positive results in Phase 3 trials in Dravet syndrome and LGS, NDA submission preparation underway for Dravet syndrome and LGS.</td>
<td>Pre-NDA meeting for Dravet syndrome with FDA expected early Q3 2016. Data from second Phase 3 Dravet syndrome trial expected in 2017. Data from second Phase 3 LGS trial expected towards the end of Q3 2016. Pre-NDA meeting for LGS with FDA expected in the second half of 2016. NDA submission expected the first half of 2017. Data from Phase 3 TSC trial expected the second half of 2017. Data from Phase 3 IS trial expected the second half of 2018.</td>
</tr>
<tr>
<td></td>
<td>Initial targets: Dravet syndrome, LGS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Follow-up target: TSC</td>
<td>Phase 3 trial in TSC underway.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>IS</td>
<td>Two-part Phase 3 trial in IS expected to commence in Q4 2016.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product/Product Candidates</td>
<td>Indication</td>
<td>Partner(s)</td>
<td>Status</td>
<td>Expected Next Steps</td>
</tr>
<tr>
<td>----------------------------</td>
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<td>------------------------------------------</td>
</tr>
<tr>
<td>GWP42006 (CBDV)</td>
<td>Epilepsy</td>
<td>We retain global rights.</td>
<td>Phase 2 trial ongoing in adults with focal seizures.</td>
<td>Phase 2 data expected in Q1 2017.</td>
</tr>
<tr>
<td></td>
<td>ASD</td>
<td></td>
<td>Phase 2 trials planned within field of ASD.</td>
<td>Phase 2 trials within field of ASD expected to commence the first half of 2017.</td>
</tr>
<tr>
<td>Intravenous GWP42003</td>
<td>NHIE</td>
<td>We retain global rights.</td>
<td>Pre-clinical. FDA orphan and fast track designation.</td>
<td>Phase 1 trial expected to commence in Q4 2016.</td>
</tr>
</tbody>
</table>

**Other Orphan Product Candidates**

<table>
<thead>
<tr>
<th>Product/Product Candidates</th>
<th>Indication</th>
<th>Partner(s)</th>
<th>Status</th>
<th>Expected Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of GWP42002 and GWP42003</td>
<td>Glioma</td>
<td>We retain global rights.</td>
<td>Phase 2a trial ongoing. FDA orphan designation.</td>
<td>Phase 2a data expected Q4 2016.</td>
</tr>
</tbody>
</table>

**Other Pipeline Product Candidates**

<table>
<thead>
<tr>
<th>Product/Product Candidates</th>
<th>Indication</th>
<th>Partner(s)</th>
<th>Status</th>
<th>Expected Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>GWP42003</td>
<td>Schizophrenia</td>
<td>We retain global rights.</td>
<td>Positive Phase 2 proof-of-concept. Approved in 28 countries (excluding the United States)</td>
<td>Data under review for next steps.</td>
</tr>
<tr>
<td>Sativex (nabiximols)</td>
<td>MS spasticity</td>
<td>Otsuka, Almirall, Novartis, Bayer, Neopharm and Ipsen.</td>
<td>Phase 2 trial ongoing.</td>
<td>Phase 2 data expected Q4 2016.</td>
</tr>
<tr>
<td></td>
<td>Cerebral Palsy spasticity</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Epidiolex® for Orphan Childhood-onset Epilepsy**

Our lead cannabinoid product candidate is Epidiolex, a liquid formulation of pure plant-derived CBD, which is in development for the treatment of a number of rare childhood-onset epilepsy disorders. Several features of the pharmacology of certain cannabinoids suggest that they may be candidates for investigation as anti-epileptic drugs, or AEDs. We have been conducting pre-clinical research of CBD in epilepsy since 2007, primarily in collaboration with the University of Reading in the United Kingdom. This research has shown that CBD has significant anti-epileptiform and anticonvulsant activity using a variety of *in vitro* and *in vivo* models and that it has the ability to treat seizures in acute animal models of epilepsy with significantly fewer side effects than existing AEDs.

Many cases of epilepsy are able to be classified and have clearly defined natural histories providing important information on the likelihood of seizure control and chance of remission. Some of the rarer electroclinical syndromes have very poor responses to treatment and negligible remission rates such as Ohtahara in neonates, Dravet syndrome in infants, LGS in young children and progressive myoclonic epilepsies in adolescence. An electroclinical syndrome is a complex of clinical features, signs and symptoms that together define a distinctive, recognizable clinical disorder,

Our strategy for the development of Epidiolex within the field of childhood-onset epilepsy is to initially concentrate formal development efforts on four orphan indications: Dravet Syndrome, LGS, TSC and IS. We have to date received Orphan Drug Designation from the FDA for Epidiolex for the treatment of Dravet.
syndrome, LGS, TSC and IS. Additionally, we have received Fast Track Designation from the FDA and Orphan Designation from the EMA for Epidiolex for the treatment of Dravet syndrome. We expect to further expand the potential market opportunity of Epidiolex by targeting additional orphan seizure disorders.

Epilepsy Market Overview

Epilepsy afflicts between 1.3 million to 2.8 million adults and children in the United States according to the Epilepsy Foundation. The Epilepsy Foundation believes its most accurate estimate is 2.2 million people, or 7.1 for every 1,000 people. According to Kwan and Brodie in the February 2000 edition of the New England Journal of Medicine, 36% of patients with epilepsy were pharmacoresistant. Of the patients in the study, 47% became seizure-free during treatment with their first AED, 13% became seizure-free during treatment with a second AED as a monotherapy, and 4% became seizure-free with a third AED or treatment with multiple AEDs. The remaining 36% of patients were classified by the authors as having pharmacoresistant epilepsy. Furthermore it is recognized that some of those that do find relief often suffer side effects severe enough with their current medication that an alternative or adjunct treatment is often sought. The costs of uncontrolled epilepsy are significant, with direct and indirect costs associated with epilepsy totaling more than $15 billion per year. It is estimated that 50,000 epilepsy related deaths occur each year, more than breast cancer deaths annually.

According to Russ et al. in the February 2012 edition of Pediatrics, there are 466,000 childhood epilepsy patients in the United States and 765,000 patients in Europe, of which 30%, or about 140,000 patients in the United States and about 230,000 in Europe, are deemed medically intractable or pharmacoresistant.

Dravet Syndrome

Dravet syndrome is a severe infantile-onset, genetic, drug-resistant epilepsy syndrome with a distinctive but complex electroclinical presentation. Onset of Dravet syndrome occurs during the first year of life with clonic seizures (jerking) and tonic-clonic (convulsive) seizures in previously healthy and developmentally normal infants. Symptoms peak at about five months of age, and the latest onset beginning by 15 months of age. Other seizures develop between one and four years of age such as prolonged focal dyscognitive seizures and brief absence seizures, and duration of these seizures decreases during this period, but their frequency increases. Prognosis is poor and approximately 14% of children die during a seizure, because of infection due, for example, to prolonged periods of physical inactivity, the presence of advanced neurodegenerative disease or a compromised level of consciousness requiring a feeding tube, or suddenly due to uncertain causes, often because of the relentless neurological decline or from Sudden Unexpected Death in Epilepsy. Patients develop intellectual disability and life-long ongoing seizures. Intellectual impairment varies from severe in 50% of patients, to moderate and mild intellectual disability each accounting for 25% of cases. Patients may rarely return to normal intellect.

According to Forsgren L. et al. in the 2004 edition of Epilepsy in Children, the incidence of epilepsy in the first year of life is 1.5 per 1,000 people, or, by our estimate, 6,450 new epilepsies per year worldwide. According to Dravet et al. in the 2012 edition of Epileptic Syndromes in Infancy, Childhood and Adolescence, up to 5% of epilepsies diagnosed in the first year of life are Dravet syndrome, equating to 320 new cases per year in the United States with a mortality rate that studies have shown may be as high as 15% in the first 20 years of life. By our estimate, there are approximately 5,440 patients with Dravet syndrome in the United States under the age of 20 years. Applying the same assumptions in Europe, we believe there are an estimated 6,710 Dravet syndrome patients in the European Union under the age of 20 years.

A large percentage of cases of Dravet syndrome have a family history for epilepsy or convulsions. Heterozygous de novo mutations of the alpha 1 (α-1) subunit of the SCN1A gene, which encodes a voltage-gated sodium channel, are the major cause of Dravet syndrome and are found in approximately 75% – 80% of patients and more than 500 SCN1A mutations have been reported to be associated with this disorder. There are currently no FDA-approved treatments specifically indicated for Dravet syndrome. The standard of care usually involves a combination of the following anticonvulsants: clobazam, clonazepam, levetiracetam, topirimate, valproic acid, ethosuximide or zonisamide. Stiripentol is approved in Europe for the treatment of Dravet syndrome in conjunction with clobazam and valproate. In the United States, stiripentol was granted an Orphan Drug Designation for the treatment of Dravet syndrome in 2008; however, the drug is not FDA approved. Potent sodium channel blockers used to treat epilepsy actually increase seizure frequency

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in patients with Dravet syndrome. The most common are phenytoin, carbamazepine, lamotrigine and rufinamide. Management of this disease may also include a ketogenic diet, and physical and communication therapy. In addition to anti-convulsive drugs, many patients with Dravet syndrome are treated with anti-psychotic drugs, stimulants and drugs to treat insomnia.

**Dravet Syndrome Phase 3 Clinical Program**

We held a pre-Investigational New Drug, or IND, meeting with the FDA in February 2014 to discuss the investigational plan for Epidiolex in Dravet syndrome, following which we opened a commercial IND in May 2014. In October 2014, we commenced a Phase 2/3 trial designed as a two-part randomized double-blind, placebo-controlled parallel group dose escalation, safety, tolerability, pharmacokinetic and efficacy trial of single and multiple doses of Epidiolex to treat Dravet syndrome in children who are being treated with other AEDs. Part One was completed in February 2015, and included pharmacokinetic and dose-finding data elements in a total of 34 patients over a 3 week treatment period.

Following a review of the Part One data by an independent panel, Part Two (Phase 3) of the trial commenced in March 2015, and was a placebo-controlled safety and efficacy evaluation of Epidiolex (at a dose of 20mg/kg per day) over a 3-month treatment period.

This Phase 3 trial randomized 120 patients into two arms, Epidiolex 20mg/kg/day (n=61) and placebo (n=59). Epidiolex or placebo was added to current AED treatment regimens. On average, patients were taking approximately three AEDs, having previously tried and failed an average of more than four other AEDs. The average age of trial participants was ten years and 30 percent of patients were younger than six years of age. The median baseline convulsive seizure frequency per month was 13.

The primary efficacy endpoint was a comparison between Epidiolex and placebo measuring the percentage change in the monthly frequency of convulsive seizures during the 14-week treatment period compared with the 4-week baseline observation period. In this trial, patients taking Epidiolex achieved a median reduction in monthly convulsive seizures of 39 percent compared with a reduction on placebo of 13 percent, which was highly statistically significant (p=0.01). A series of sensitivity analyses of the primary endpoint confirmed the robustness of this result. The difference between Epidiolex and placebo emerged during the first month of treatment and was sustained during the entire treatment period. Results from secondary efficacy endpoints reinforced the overall effectiveness observed with Epidiolex.

Epidiolex was generally well tolerated in this trial. The most common adverse events (occurring in greater than 10 percent of Epidiolex-treated patients) were: somnolence, diarrhea, decreased appetite, fatigue, pyrexia, vomiting, lethargy, upper respiratory tract infection and convulsion. Of those patients on Epidiolex that reported an adverse event, 84 percent reported it to be mild or moderate. Ten patients on Epidiolex experienced a serious adverse event compared with three patients on placebo. Eight patients on Epidiolex discontinued treatment due to adverse events compared with one patient on placebo. We are working with the investigators in this trial on a manuscript for peer-review publication. We expect this paper will be published in the fourth quarter of 2016.

In addition to this first Phase 3 trial, we are conducting a second Phase 3 trial of Epidiolex in Dravet syndrome which is expected to recruit 150 patients. This placebo-controlled trial differs from the first Phase 3 trial in that it includes two Epidiolex dose arms, at 20mg/kg per day and at 10 mg/kg per day. We continue to work to enroll this trial and expect to report results from the trial in 2017. Each of these trials will be the largest known controlled trials in Dravet syndrome.

**Lennox-Gastaut Syndrome**

LGS is a type of epilepsy with multiple types of seizures, particularly tonic (stiffening) and atonic (drop) seizures. According to Trevathan et al. in the December 1997 edition of Epilepsia, the estimated prevalence of LGS is between 3% and 4% of childhood epilepsy with the cause of the disorder unknown in 1 out of 4 children. LGS affects between 14,500 – 18,500 children under the age of 18 years in the United States and over 30,000 children and adults in the United States. Eighty percent of children with LGS continue to experience seizures, psychiatric, and behavioral deficits in adulthood. Seizures due to LGS are hard to control and they generally require life-long treatment as LGS usually persists into the adult years. Historically patients...
with LGS have had few effective treatment options. Intellectual and behavioral problems associated with LGS are common and add to the complexity of this syndrome and the difficulties in managing life with LGS.

Drug resistance is one of the main features of LGS. Generally, treatment often requires broad spectrum AEDs and/or polypharmacy. Treatment will also depend on the seizure type as some treatments that are effective for one type of seizure may worsen another. The FDA approved treatments for LGS are: Onfi (clobazam); Banzel (rufinamide); Lamictal (lamotrigine); Topamax (topiramate); and Felbatol (felbamate). These medicines are often used as adjunctive therapy with existing medications. When used with other particular AEDs, the FDA approved treatments for LGS show a level of efficacy, however, many also have severe undesirable side effects. Furthermore, several of these medicines are based on the same mechanism of action as traditional AEDs. As patients with LGS generally need to take several treatments to gain any change to their seizure frequency, we believe that there is a need for further pharmacological treatments, particularly those with a different mechanism of action, to give prescribers more options in treating this rare, pharmacoresistant syndrome.

**LGS Phase 3 Clinical Program**

In April 2015, we commenced a Phase 3, randomized, double-blind placebo-controlled trial to evaluate the safety and efficacy of Epidiolex for the treatment of LGS in patients who are being treated with other AEDs. Patients aged two to 55 years with a confirmed diagnosis of drug-resistant LGS currently uncontrolled on one or more concomitant AEDs were eligible to participate in this trial. The trial randomized 171 patients into two arms, where Epidiolex 20mg/kg/day (n=86) or placebo (n=85) was added to current AED treatment. On average, patients were taking approximately 3 AEDs, having previously tried and failed an average of 6 other AEDs. The average age of trial participants was 15 years (34% were 18 years of age or older). The median baseline drop seizure frequency per month was 74.

The primary efficacy endpoint of this trial was a comparison between Epidiolex and placebo in the percentage change in the monthly frequency of drop seizures during the 14 week treatment period (2 week dose escalation period followed by 12 weeks of maintenance) compared to the 4 week baseline period before randomization. Drop seizures were defined as atonic, tonic and tonic-clonic seizures involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient’s head on a surface. During the treatment period, patients taking Epidiolex achieved a median reduction in monthly drop seizures of 44% compared with a reduction of 22% in patients receiving placebo, and the difference between treatments was statistically significant (p=0.0135). A series of sensitivity analyses of the primary endpoint confirmed the robustness of this result. The difference between Epidiolex and placebo emerged during the first month of treatment and was sustained during the entire treatment period. The results from secondary efficacy endpoints reinforced the overall effectiveness observed with Epidiolex.

Epidiolex was generally well tolerated in this trial. Overall, 86% of all Epidiolex patients experienced an adverse event compared with 69% of patients on placebo. The most common adverse events (occurring in greater than 10% of Epidiolex-treated patients) were: diarrhea, somnolence, decreased appetite, pyrexia, and vomiting. Of those patients on Epidiolex who reported an adverse event, 78% reported it to be mild or moderate. Twenty patients on Epidiolex experienced a serious adverse event (nine of which were deemed treatment related) compared with four patients on placebo (one of which was deemed treatment related). Twelve patients on Epidiolex discontinued treatment due to adverse events compared with one patient on placebo. There was one death in the Epidiolex group, which was deemed unrelated to treatment. Of the patients who completed this trial, 100% have opted to continue into an open-label extension trial.

We expect data from this trial and selected other trials to be submitted for presentation at the Annual Meeting of the American Epilepsy Society in December 2016.

In addition to this first Phase 3 trial of Epidiolex in LGS, we are conducting a second Phase 3 dose-ranging trial of Epidiolex for the treatment of LGS, which is fully enrolled at 225 patients. This second trial has three treatment arms: Epidiolex 20mg/kg/day and 10mg/kg/day and placebo. We expect to report top-line results from this trial towards the end of the third quarter of 2016.
**Tuberous Sclerosis Complex (TSC)**

TSC is a genetic disorder that causes non-malignant tumors to form in many different organs, primarily in the brain, eyes, heart, kidney, skin and lungs. The brain and skin are the most affected organs. TSC results from a mutation in tumor suppression genes TSC1 or TSC2. According to the Tuberous Sclerosis Alliance, TSC is estimated to affect approximately 50,000 patients in the United States. The most common symptom of TSC is epilepsy, which occurs in 75 – 90% of patients, about 70% of whom experience seizure onset in their first year of life. Approximately 60% of these TSC patients (or approximately 25,000 of patients in the United States) have treatment-resistant seizures. The seizures of TSC are typically focal in onset, meaning that they are localized to one hemisphere of the brain. There are significant co-morbidities associated with TSC including cognitive impairment in 50%, autism spectrum disorders in up to 40% and neurobehavioral disorders in over 60% of individuals with TSC.

A number of patients with TSC have been treated with Epidiolex in the expanded access program (as explained in detail below). At the 69th Annual Meeting of the American Epilepsy Society in December 2015, safety and efficacy data on 10 patients diagnosed with TSC from the physician-led open-label Epidiolex expanded access program were presented by Massachusetts General Hospital for Children (Geffrey et al 2015). The percent of patients who reported a 50% or greater reduction in seizures were 50%, 50%, 40%, 60% and 66% at 2, 3, 6, 9, and 12 months of treatment with Epidiolex, respectively. Side effects were seen in five patients (50%) and most were resolved with AED or CBD dose adjustments.

**TSC Phase 3 Clinical Program**

In April 2016, we commenced a Phase 3 trial of Epidiolex in patients with TSC. This dose-ranging trial is a 16-week comparison of Epidiolex versus placebo in a total of approximately 200 patients, aged one to 65 years, to assess the safety and efficacy of Epidiolex as an adjunctive anti-epileptic treatment. The primary measure of this trial is the percentage change from baseline in seizure frequency during the treatment period. Primary endpoint seizures include focal motor seizures with or without impairment of consciousness or awareness and generalized convulsive seizures. We expect to report data from this trial in the second half of 2017.

**Infantile Spasms (IS)**

According to the National Institute of Neurological Disorders and Stroke, an infantile spasm is a specific type of seizure seen in an epilepsy syndrome of infancy and childhood known as West syndrome. West syndrome is characterized by infantile spasms, developmental regression, and a specific pattern on electroencephalography, or EEG, testing called hypsarrhythmia (chaotic brain waves). The onset of infantile spasms is usually in the first year of life, typically between 4 to 8 months of age. The seizures primarily consist of a sudden bending forward of the body with stiffening of the arms and legs; some children arch their backs as they extend their arms and legs. Spasms tend to occur upon awakening or after feeding, and often occur in clusters of up to 100 spasms at a time. Infants may have dozens of clusters and several hundred spasms per day. Many underlying disorders, such as birth injury, metabolic disorders, and genetic disorders can give rise to spasms, making it important to identify the underlying cause. In some children, no cause can be found.

According to data published on Medscape, the condition constitutes 2% of childhood epilepsies and 25% of epilepsies with onset in the first year of life. There are approximately 2,000 to 4,000 new cases in the United States each year. Cognitive and developmental delay is severe in 70% of patients, often with psychiatric problems such as autistic features or hyperactivity. IS usually stops by five years of age, but may be replaced by other seizure types. It has been found that 50% to 70% of patients develop other seizure types and that 18 to 50% will develop LGS or some other form of symptomatic generalized epilepsy. The long-term prognosis is poor and includes increased mortality and severe neurodevelopmental impairment.

The FDA approved treatments for IS are ACTH (Acthar Gel) and vigabitrin (Sabril). These treatment options are successful in 20% to 80% of patients. Both of these medicines have significant adverse events, including boxed warnings limiting their long-term use.

On December 7, 2015, at the Annual Meeting of the American Epilepsy Society, safety and efficacy data on 9 patients suffering from epileptic spasms from the Epidiolex expanded access program were presented by
Massachusetts General Hospital for Children (Abati et al.). Epilepsy spasms often remain refractory to standard AEDs. According to this poster, Epidiolex exerted its effects in a short time course, with a response rate of 67% after two weeks and 78% after one month. Three of nine patients became spasm-free after two weeks of Epidiolex treatment. By parent report, patients also showed cognitive gains including improvements in alertness, verbal capacity/communication, and cognitive availability.

**IS Phase 3 Clinical Program**

We expect to commence a two-part Phase 3 trial of Epidiolex in patients with IS in the fourth quarter of 2016. We expect to report data from this trial in the second half of 2018.

**Cannabinoid Rationale for Treating Epilepsy**

Several features of the pharmacology of certain cannabinoids suggest that they may be candidates for investigation as AEDs. A series of validated laboratory experiments have shown that certain cannabinoids can modulate neurotransmission, can reduce neuroinflammation and can affect oxidative stress. These cannabinoids may simultaneously modulate a number of endogenous systems to attenuate and/or prevent epileptic neuronal hyperexcitability. These include ion channel control, inflammation, modulation of oxidative stress and inhibition of gene expression of epilepsy-associated genes.

Several different ion channels influence epileptogenesis (the process by which a normal brain develops epilepsy) including both ligand-gated and voltage-gated ion channels. It is the former to which a proportion of the actions of plant cannabinoids can be attributed, for example through agonism and antagonism of G-protein coupled receptors, including orphan receptors as well as modulation of transient receptor potential (TRP) channels (differentially activated, repressed and desensitized by different plant cannabinoids). Additionally it is now recognized that there is a role for inflammation in epilepsy. Some cannabinoids possess anti-inflammatory properties including inhibition of pro-inflammatory cytokine release and modulation of glial cell/neuronal interactions. Furthermore cannabinoids modulate oxidative stress and production of toxic nitric oxide. Research shows that other than THC, most plant cannabinoids have little or no affinity for the cannabinoid receptors, and therefore do not share the unwanted psychoactivity that goes along with stimulation of the CB1 receptor in particular.

Finally, certain cannabinoids may possess disease modifying potential through regulation of epilepsy-related genes, as well as up-regulation of endogenous anti-convulsant neuropeptides and/or compensatory systems.

Based on recent findings in The Journal of Pharmacology and Experimental Therapeutics, CBD is likely to be acting via more than one mechanism of action with the effect of reducing neuronal hyperexcitability. Neuronal hyperexcitability occurs when the nerve keeps firing and can lead to seizures. There are several mechanisms that aim to stop nerves firing once they have stimulated the postsynaptic nerve. Among these mechanisms is the movement of positively charged ions, e.g. sodium and calcium, across the cell membrane in a process called re-polarization. If these mechanisms are faulty, then the continued firing means ‘hyperexcitability’. Importantly, the anti-seizure effects of CBD are not dependent on cannabinoid receptors, nor on sodium channels.

**CBD Pharmacology in Epilepsy**

The epilepsy-relevant pharmacology of CBD can be summarized as follows: inhibition of neutrophil and microglial migration, anti-inflammatory effects in conventional animal models; inhibition of adenosine uptake and indirect agonism of the neuroprotective and anti-inflammatory A2a receptor; other neuroprotective effects (TNF inhibition and anti-oxidant activity); antipsychotic activity; agonism at the orphan receptor GPR55; desensitizer of TRP channels; anticonvulsant activity in all laboratory models tested; ion channel modulation; reduction of acetylcholine turnover at neuro-muscular junctions; and perturbation of the negative effects of THC (opposes euphoric, cognitive and psychotropic effects) via one or more of the above mechanisms.

There is a significant effort to identify the mechanisms of action that underpin the clinical effectiveness of Epidiolex (and other cannabinoids) in epilepsy, including investigation of the effects of cannabinoids on epilepsy associated gene expression. CBD has negligible binding at the CB1 receptor, and so shares neither the pharmacology of CB1 agonists such as THC nor that of CB1 inverse agonists such as Rimonabant. CBD’s
mechanism for treating seizures is not fully understood but is believed to involve a combination of beneficial effects stacking upon one another (polypharmacology).

Preclinical models suggest a broad role for CBD in generalized and partial seizures, and clinical reports of benefit extend into other congenital seizure disorders.

Our CBD Pre-Clinical Research in Pediatric Epilepsy

We have conducted pre-clinical research of CBD in epilepsy for several years and have reported significant anti-epileptiform and anticonvulsant activity using a variety of in vitro and in vivo models. This research has shown the ability of CBD to treat seizures in acute models of epilepsy with significantly fewer side effects than existing AEDs. Our cannabinoid research compounds were screened in electrically discharging hippocampal brain slices caused by the omission of Mg2+ ions from, or addition of the K+ channel blocker, 4-aminopyridine (4-AP) to the bathing solution. In these models, 100μM of CBD decreased epileptiform amplitude and duration as well as burst frequency; importantly, this compound exerted no effect upon the propagation of epileptiform activity.

Subsequently, the anti-convulsant actions of 1, 10 and 100 mg/kg of CBD were examined in three different in vivo seizure rodent models. In the Pentylenetetrazol (PTZ) induced acute, generalized seizures model, 100 mg/kg of CBD significantly decreased mortality rate and the incidence of tonic-clonic seizures. In the acute pilocarpine model of temporal lobe seizures all doses of CBD significantly reduced the percentage of animals experiencing the most severe seizures. In this model of partial seizures, 10 and 100 mg/kg of CBD significantly decreased the percentage of animals dying as a result of seizures and all doses of CBD also decreased the percentage of animals experiencing the most severe tonic-clonic seizures.

During 2013, we received increasing interest among U.S. pediatric epilepsy specialists and patient organizations in the potential role of CBD in treating intractable childhood epilepsy, in particular Dravet syndrome. This interest led to a medical conference organized by the New York University School of Medicine on October 4, 2013 titled: “Cannabidiols: Potential Use in Epilepsy and Other Neurological Disorders.” Epilepsy specialists at the meeting viewed CBD as attractive for the treatment of these disorders for a variety of reasons, including:

- Case reports of its efficacy in severe, refractory patients consistently provide encouraging signals; and
- CBD’s “natural” profile and safety data generated to date suggest that it could be an attractive treatment option without the unwanted side effects of other AEDs.

In addition, specialists at this conference concluded the following:

- Only a pharmaceutical formulation of CBD which could meet FDA requirements for standardization and quality control would be appropriate for administering to children; and
- Placebo-controlled trials should be performed as a matter of urgency in order to provide robust evidence of the safety and efficacy of CBD.

Epidiolex Expanded Access INDs

In parallel with our commercial clinical trial programs, the FDA has been receiving and approving INDs from independent investigators in the United States to allow treatment with Epidiolex in children and young adults with a range of epilepsy syndromes. To date, the FDA has granted 20 intermediate expanded access INDs to independent physician investigators in the United States to treat a total of 465 children and young adults suffering from intractable epilepsy with Epidiolex. In addition, the FDA has granted further INDs to treat 455 additional patients under expanded access programs supported by six U.S. states and for which we are supplying Epidiolex. The FDA may authorize expanded access programs to facilitate access to investigational drugs for treatment use for patients with a serious or immediately life-threatening disease or condition who lack therapeutic alternatives. The patients in these INDs suffer not only from Dravet syndrome, LGS, TSC and IS but also from other pediatric epilepsy syndromes. The FDA has also authorized to physicians twelve individual emergency INDs and three individual patient non-emergency INDs. Outside the United States, the government of New South Wales, Australia, is collaborating with us on separate state-based clinical trials in epilepsy and establishing its own compassionate access scheme.
On December 23, 2015, Epidiolex data from the physician-led expanded access program in treatment-resistant epilepsy were published by the treating physicians in The Lancet Neurology (Devinsky et al., Cannabidiol in Patients with Treatment Resistant Epilepsy: an open-label interventional trial, Lancet Neurology December 23, 2015). This paper provides a more expansive description of data previously presented at the American Academy of Neurology Annual Meeting in April 2015. Data in the paper are from 11 independent epilepsy centers in the United States; 162 patients who had at least 12 weeks of follow-up after the first dose of cannabidiol were included in the safety and tolerability analysis, and 137 patients were included in the efficacy analysis. Of these 162 patients, there were 33 patients with Dravet syndrome and 31 patients with LGS. The published paper reported that Epidiolex reduced seizure frequency across multiple drug-resistant epilepsy syndromes and seizure types and was generally well tolerated. In the paper the authors note that the administration of Epidiolex as an add-on treatment led to a clinically meaningful reduction in seizure frequency in many patients and had an adequate safety profile in this patient population with highly treatment-resistant epilepsies. The safety and tolerability profile of Epidiolex was favorable with only 3 percent of patients terminating therapy due to an adverse event. Highlights from the publication of particular relevance to GW’s pivotal trial programs in Dravet syndrome and LGS include:

- **Dravet syndrome**: The median reduction in monthly motor (i.e., convulsive) seizures was 49.8% (n=32). 50% of Dravet syndrome patients had a 50% or greater reduction in monthly motor seizures. During the last 4 weeks of therapy, 13% (n=4) were free of motor seizures; these patients were also free of all other seizure types. In Dravet syndrome patients who experienced them at baseline, there was a median 69.2% reduction in monthly tonic seizures (n=6), 46.7% reduction in monthly tonic-clonic seizures (n=29), and 83.3% reduction in non-motor focal seizures (n=10).

- **LGS**: A median 68.8% reduction in average monthly atonic seizures was observed (n=14). During the last 4 weeks of therapy, 21% (n=3) were free of atonic seizures and 3% (n=1) were totally seizure free. In LGS patients who experienced motor and tonic seizures at baseline, there were median 36.8% (n=30) and 44% (n=21) reductions, respectively.

- Clobazam co-therapy was associated with a higher rate of treatment response (median reduction in convulsive seizures): 56.4% v. 35.0% at week 12; this may reflect elevations in the N-desmethyl clobazam metabolite. This apparent effect of clobazam co-therapy was not seen in Dravet syndrome or LGS groups — at week 12, 53% of Dravet/LGS patients on Clobazam were 50% responders compared with 54% not taking Clobazam (odds ratio 0.97 (95% Confidence Interval — 0.35 – 2.65)).

- Adverse events occurred in 79% of all patients treated with cannabidiol (n=162). Adverse events reported in greater than 10% of patients were somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%) and convulsion (11%). Most adverse events were mild or moderate and transient. Five patients (3%) discontinued treatment due to an adverse event.

- Serious adverse events were reported in 48 patients (30%), including one death, regarded as unrelated to CBD. Serious adverse events which were deemed possibly related to CBD occurred in 20 patients.

The authors noted that without a control group, the results regarding efficacy and safety should be interpreted cautiously.

**The American Epilepsy Data**

In addition to the data published in The Lancet Neurology, seven abstracts related to the physician-led expanded access program for Epidiolex in treatment-resistant epilepsy were presented at the 69th Annual Meeting of the American Epilepsy Society including data from the physician-led Epidiolex expanded access program. On December 7, 2015, at the Annual Meeting of the American Epilepsy Society, physician reports of clinical effect and safety data was presented on 261 children and young adults with treatment-resistant epilepsy who had been treated with Epidiolex for a period of at least 12 weeks (Devinsky et al.). This data is from 16 clinical sites in the United States and was generated under the expanded access program. In addition,
physician reports of safety data were presented on 313 patients (261 patients with 12 weeks treatment effect data plus an additional 52 patients still in their first 12 weeks of treatment or who withdrew from treatment).

The patients included in the Epidiolex program had Dravet syndrome (17% of the total) and LGS (15% of the total), as well as 14 other types of severe epilepsy, such as TSC, Aicardi syndrome and Doose syndrome. Many of these other types of epilepsy are severe and rare, and several patients with these epilepsies have major congenital structural brain abnormalities.

The 261 patients were predominately children with an average age of 11.8 years. In all cases, Epidiolex was added to current AED treatment regimes. On average, patients were taking approximately three other AEDs. At baseline, the median number of convulsive seizures per month was 31.

**Clinical Effect Data — All Patients**

Data was presented on all 261 patients who had at least 12 weeks treatment. Treatment was open label. Of these 261 patients, 135 patients had also reached 36 weeks treatment at the time of data analysis. Information collected on all seizures (convulsive and non-convulsive) was reported for each patient. The following data was presented showing the median change in seizure frequency compared to a 4-week baseline period.

<table>
<thead>
<tr>
<th>Week</th>
<th>Median change in seizure frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>33.5%</td>
</tr>
<tr>
<td>8</td>
<td>42.5%</td>
</tr>
<tr>
<td>12</td>
<td>45.1%</td>
</tr>
<tr>
<td>16</td>
<td>49.5%</td>
</tr>
<tr>
<td>24</td>
<td>45.9%</td>
</tr>
<tr>
<td>36</td>
<td>-44.1%</td>
</tr>
</tbody>
</table>

At the end of 12 weeks, 47% of all patients experienced a ≥50% reduction in seizures and 9% of all patients were seizure-free.

At the end of 12 weeks, the median overall reduction in convulsive seizure frequency was 48.8%.

**Clinical Effect Data — Dravet syndrome patients only**

Data was presented on 44 patients with Dravet syndrome who had at least 12 weeks treatment data. Of these 44 patients, 25 patients had also reached 36 weeks treatment at the time of data analysis. Information collected on all seizures (convulsive and non-convulsive) was reported for each patient. The following data was presented showing the median change in seizure frequency compared to a 4-week baseline period.

<table>
<thead>
<tr>
<th>Week</th>
<th>Median change in seizure frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>36.8%</td>
</tr>
<tr>
<td>8</td>
<td>56.4%</td>
</tr>
<tr>
<td>12</td>
<td>62.7%</td>
</tr>
<tr>
<td>16</td>
<td>56.2%</td>
</tr>
<tr>
<td>24</td>
<td>55.4%</td>
</tr>
<tr>
<td>36</td>
<td>-50.6%</td>
</tr>
</tbody>
</table>

At the end of 12 weeks, 13% of Dravet syndrome patients were seizure-free.

Of the 44 patients with Dravet syndrome, 42 patients had convulsive seizures at baseline. At the end of 12 weeks, the median reduction in convulsive seizures in these patients was 52.3%.

**Clinical Effect Data — Patients without Dravet syndrome**

Data was made available on all 217 patients with diagnoses other than Dravet syndrome who had at least 12 weeks treatment. Of these 217 patients, 110 patients had also reached 36 weeks treatment at the time of data analysis. Information collected on all seizures (convulsive and non-convulsive) was reported for each patient. The following data was presented showing the median change in seizure frequency compared to a 4-week baseline period.

<table>
<thead>
<tr>
<th>Week</th>
<th>Median change in seizure frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>33.3%</td>
</tr>
<tr>
<td>8</td>
<td>41.2%</td>
</tr>
<tr>
<td>12</td>
<td>41.4%</td>
</tr>
<tr>
<td>16</td>
<td>47.0%</td>
</tr>
<tr>
<td>24</td>
<td>45.5%</td>
</tr>
<tr>
<td>36</td>
<td>-44.1%</td>
</tr>
</tbody>
</table>

**Clinical Effect Data — LGS patients only**

Data was presented on 40 patients with LGS who had at least 12 weeks treatment data. Of these patients, 14 had atonic seizures at baseline. In these patients, there was a 71.1% median reduction in the number of atonic seizures at the end of 12 weeks.

**Safety Data**

Safety data was made available on 313 patients (261 patients with 12 weeks treatment effect data plus 52 additional patients for whom 12 week treatment effect data is not yet available or who withdrew from
treatment) and represents approximately 180 patient-years of exposure to Epidiolex. The most common adverse events (occurring in 10% or more of patients and resulting from all causes) were somnolence (23%), diarrhea (23%), fatigue (17%), decreased appetite (17%), convulsions (17%) and vomiting (10%). Adverse events led to discontinuation in four percent of patients. Most adverse events were mild or moderate and transient. 14 patients (4%) reported an adverse event leading to discontinuation. There were 36 (12%) withdrawals from treatment due to lack of clinical effect. Serious adverse events were reported in 106 patients. Of these, serious adverse events in 16 (5%) patients were deemed possibly related to treatment, including altered liver enzymes (4 patients), status epilepticus/convulsion (4), diarrhea (4), decreased weight (3), thrombocytopenia (1). Serious adverse events reported under the expanded access program include seven deaths. We are also aware of the death of one patient that received Epidiolex on a compassionate use basis in the United Kingdom. All eight of these deaths have been investigated and were all deemed unrelated to Epidiolex by the independent investigators.

Since the time that this data was collected in September 2015, there have been four more deaths reported under the expanded access program. We are also aware of the death of one additional patient who received Epidiolex on a compassionate use basis in the United Kingdom. Outside of these programs, there was one patient death during our recently completed Phase 3 trial of Epidiolex in LGS, and five patient deaths during the open label extension trial for patients who have completed their treatment under our completed or ongoing Phase 3 trials of Epidiolex in Dravet syndrome and LGS. All eleven of these deaths have been investigated and all of them have been deemed unrelated to treatment with Epidiolex by the independent investigators.

**Note Regarding Expanded Access Studies**

The expanded access studies we are currently supporting are uncontrolled, carried out by individual physician investigators independent from us, and not always conducted in strict compliance with Good Clinical Practices, all of which can lead to an observed treatment effect that may differ from one seen in placebo-controlled trials. Data from these studies provide only anecdotal evidence of efficacy for regulatory review, although they may provide supportive safety information for regulatory review. The patients treated under these expanded access INDs contain no control or comparator group for reference and these patient data are not designed to be aggregated or reported as study results. Moreover, data from such small numbers of patients may be highly variable. Information obtained from these INDs, including the statistical principles that the independent investigators have chosen to apply to the data, may not reliably predict data collected via systematic evaluation of efficacy in our sponsored clinical trials, or evaluated via other statistical principles that may be applied in these trials. We can offer no assurances that the observations reported by the treating physicians under these expanded access INDs are due solely to Epidiolex and not as a result of other factors, such as a beneficial or synergistic drug-drug interaction, as postulated above. Further, due to the non-normal distribution of the data collected from the small sample size, we have chosen to use median data in its analysis. However, other statistical principles may be more appropriate to the analysis of the clinical data generated from our placebo controlled trials of Epidiolex for the treatment of Dravet syndrome, LGS, TSC and IS.

We believe the data we have received to date under these expanded access INDs support the continued investigation of Epidiolex as a potential treatment for epilepsy, including for Dravet syndrome, LGS, TSC and IS.

**Emergency INDs**

The FDA has also granted to physicians 12 individual emergency INDs. An emergency IND is an IND for the use of an investigational new drug or biological product for clinical treatment of a patient in an emergency situation. In order to be granted an emergency IND the following five conditions must all be met: (1) the patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; (2) FDA must determine that the patient cannot obtain the drug under another IND or protocol; (3) the potential benefits to the patient justify the potential risks of the treatment and the risks from this investigational treatment are not unreasonable in the context of the disease or condition treated with this investigational product; (4) providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use; and (5) the physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition. In these cases, we have responded to, and the
FDA has approved, emergency treatment requests from physicians for children hospitalized as a result of severe and potentially life-threatening seizures. In a poster at the American Epilepsy Society annual meeting in December 2014, Lopez C. et al. presented information on a four year old patient with super refractory status epilepticus due to febrile infection related epilepsy syndrome, or FIRES, treated with Epidiolex under an emergency IND concluding that CBD was very well tolerated and associated with a significant improvement in clinical and electrographic seizure burden. We believe eight of the children treated under emergency INDs remain on Epidiolex treatment. Two children treated under emergency INDs died while receiving treatment with Epidiolex and two withdrew due to lack of efficacy; both deaths were deemed unrelated to Epidiolex by the independent investigators.

**Collaborations with State Governments in Australia**

In October 2015, we announced that we had signed a Memorandum of Understanding, or MOU, with the Government of New South Wales, or NSW, in Australia to advance a research program for Epidiolex and CBDV in children with severe, drug resistant childhood epilepsy. With respect to Epidiolex, the MOU will facilitate (i) a compassionate access program for Epidiolex, (ii) provision for NSW to host additional Phase 3 clinical trials of Epidiolex and (iii) a Phase 4 clinical trial of Epidiolex (to follow completion of the Phase 3 trials).

In June 2016, we signed an MOU with the Queensland Government in Australia to advance research into the use of cannabinoid-based pharmaceutical products for the treatment of patients in Queensland with serious illness, including childhood epilepsy. The MOU will facilitate (i) establishing a centre to undertake clinician led observational studies using cannabinoid-based investigational medicinal products across a range of childhood developmental disorders, (ii) an expanded access treatment protocol using Epidiolex for a small number of patients with severe drug-resistant epilepsy and (iii) an observational study for a small number of patients with severe drug-resistant epilepsy using Epidiolex and other cannabinoids.

**Epidiolex Manufacturing**

We are currently manufacturing Epidiolex through utilization of in-house and external third party facilities for various steps in the production process. We expect to satisfy near-term requirements for Epidiolex from these current facilities but we are also in the process of scaling-up various parts of the production process both in-house and with external third parties.

We are actively scaling our growing and manufacturing of Epidiolex to meet anticipated commercial demand, if approved. From our extensive experience in growing CBD botanical raw material, we are able to utilize a range of growing methods to generate significant quantities of CBD botanical raw material derived from our proprietary CBD plant chemotypes. In 2015, our production of CBD botanical raw materials increased by a factor of approximately 20 times (4 Tonnes to 92 Tonnes) compared with the previous year and is expected to double in 2016. This equates to approximately 200 Tonnes of CBD raw materials in 2016 and when purified and formulated, results in approximately 1.6 million 100mg/ml bottles of Epidiolex. To put this into context, in 2015, we shipped just over 20,000 bottles of Epidiolex to clinics in the United States for both controlled trials and expanded access use. With expectations of significant demand for Epidiolex upon potential approval, we plan to continue expansion of our Epidiolex plant growing capacity well beyond this 2016 goal. The finished product, Epidiolex, is a liquid formulation of pure CBD and there are several processing steps beyond growing to ensure that the product is pure, meets the required FDA specification, and can be manufactured at scale to current Good Manufacturing Practice Regulations. Each step has already been scaled and a further increase in scale of the processes is anticipated during 2016. We believe we are on track to be ready for FDA pre-approval inspection anticipated in the second half of 2017.

**Epidiolex Commercialization**

We are planning to commercialize Epidiolex in the United States and elsewhere using our own sales and marketing organization. In June 2015, we appointed Julian Gangolli to the newly created position of President, North America and he has been appointed to our Board of Directors. Mr. Gangolli is leading our commercial organization in the United States. We have also recruited a number of U.S. medical affairs, clinical trials and commercial staff, many of whom have strong epilepsy knowledge and experience. We expect this organization to expand over the next 12 months. The creation of the medical affairs team has allowed us to open scientific and consultative communications with key stakeholders, such as the patient and physician communities in the United States. Our commercial staff have begun actively developing our commercial strategy for the United States.
Our U.S. commercial organization is based in our office at Carlsbad, CA. With the successful results from the first Dravet syndrome and LGS Phase 3 trials, we are now accelerating plans for our potential U.S. commercialization of Epidiolex. We expect to implement a “high efficiency” commercial deployment model expected to include a dedicated sales force of approximately 50 to 55 sales professionals targeting approximately 4,000 – 5,000 U.S. physicians. This commercial organization will be defined by a “high-touch” patient, payer and physician communication, education and distribution model, and one in which the medical affairs organization will play a significant role in establishing strong relationships with physicians and patient organizations.

We believe that the U.S. physician awareness and enthusiasm for a new therapeutic alternative for the treatment of pediatric epilepsies is high, and that, if approved, Epidiolex would represent a new class of anti-convulsant with a potentially differentiated side-effect profile and mechanism of action.

We will commercialize our CBD-containing products for the treatment of epilepsy under a different name than Epidiolex in the United States. We will also not commercialize these products, and any of our other products, in the United States under the name GW Pharmaceuticals and will change the name of our U.S. subsidiary responsible for commercializing these products in the United States to something other than GW Pharmaceuticals Inc.

**Epidiolex Intellectual Property**

In addition to orphan exclusivity, we have been seeking to protect Epidiolex through our patent portfolio. Patent applications are being prosecuted in the United States and at the European Patent Office.

**GWP42006 (CBDV) in Epilepsy and Autism Spectrum Disorders (ASD)**

In addition to Epidiolex, our product candidates also include GWP42006, which features CBDV as the primary cannabinoid. CBDV is similar in chemical structure to CBD and has also shown anti-epileptic properties across a range of *in vitro* and *in vivo* models of epilepsy. In a paper published in the September 2012 issue of The British Journal of Pharmacology by scientists with whom we collaborate at the University of Reading, United Kingdom, GWP42006 was reported to have the potential to prevent more seizures, with few of the side effects caused by many existing AEDs, such as uncontrollable shaking. In the study, GWP42006 strongly suppressed seizures in six different experimental models commonly used in epilepsy treatment. GWP42006 was also found to provide additional efficacy when combined with drugs currently used to control epilepsy. Genetic biomarkers for response have been identified.

We have also evaluated GWP42006 in both general and syndromic pre-clinical models of ASD yielding promising signals on cognitive and social endpoints as well as repetitive behavior. These animal models include both genetically determined abnormalities of neurobehavioral, and chemically-induced models, and include Rett syndrome and Fragile X among others.

We have completed a Phase 1 trial of GWP42006 in 66 healthy subjects. In this trial, GWP42006 was well tolerated even at the highest tested dose. There were no serious or severe adverse events reported, nor any withdrawals due to adverse events.

We are pursuing multiple development programs for GWP42006 both within adult and childhood epilepsy and in childhood behavioral disorders:

- In epilepsy, we are recruiting a Phase 2 trial of GWP42006. This is a double-blind, randomized, placebo-controlled two-part trial to investigate the pharmacokinetics, followed by efficacy and safety of GWP42006 as add-on therapy in patients with inadequately controlled focal seizures. The first part of this trial has completed enrollment of 32 patients and the dose-ranging pharmacokinetic and safety data has been reviewed by an independent panel. We have commenced the efficacy part of the trial and expect to recruit an additional 100 patients. Data from this part of the trial is expected in the first quarter of 2017.

- As described above, in October 2015, we announced that we had signed a MOU with the NSW Government in Australia to advance a research program for Epidiolex and CBDV in children with severe, drug resistant childhood epilepsy. The MOU will facilitate a world first, Phase 2 clinical trial in children for GWP42006.

- We are conducting pre-clinical research into CBDV within the field of ASD. Many of the pediatric
intractable epilepsy conditions within the Epidiolex expanded access program share considerable overlap with ASD and these conditions often fall within the orphan disease space. Initial clinical observations from treating physicians suggest a potential role for cannabinoids in addressing problems associated with ASD such as deficits in cognition, behavior and communication.

We are working with investigators and early open-label clinical experience under the MOU is expected to commence in the second half of 2016, with Phase 2 placebo-controlled trials expected to commence in the first half of 2017.

CBDV Intellectual Property Portfolio

Several CBDV patents have been filed.

Other Orphan Product Candidates

Neonatal Hypoxic-Ischemic Encephalopathy (NHIE)

NHIE is acute or sub-acute brain injury due to asphyxia caused during birth resulting from deprivation of oxygen during birth, referred to as hypoxia, as a result of a sentinel event such as ruptured placenta, parental shock and even increased heart rate. Hypoxic damage can occur to most of the infant’s organs, but brain damage is the most serious and least likely to heal, resulting in encephalopathy. This can later manifest itself as either mental retardation (including developmental delay and/or intellectual disability) or physical disabilities such as spasticity, blindness and deafness. Indeed, spastic diplegia and the other forms of cerebral palsy almost always feature asphyxiation during the birth process as a contributing factor. The exact timing and underlying causes of these outcomes remains unknown but it is widely recognized that interventions need to be administered within six hours of hypoxic insult.

Market Overview

According to Kurinczuk et al. in the 2010 edition of Early Human Development, the incidence of NHIE is 1.5 to 2.8 per 1,000 births in the United States, or, by our estimate, 6,500 to 12,000 cases per year. Of these, 35% are expected to die in early life and 30% of cases will result in permanent disability. There are currently no FDA-approved medicines specifically indicated for NHIE. The only FDA-approved treatment is the Olympic Cool-Cap System and treatment guidelines in many European countries also support use of whole body hypothermia. Clinical trials have shown the Cool-Cap to reduce the occurrence of disability due to NHIE but not death, while whole body hypothermia had a more marginal effect on disability but is able to reduce mortality. This treatment is only available in specialized neonatal intensive care units and must be started within 6 hours of birth. Even if a patient is put into induced hypothermia there is still a significant rate of morbidity and mortality, with a meta-analysis of the available data revealing a 27% death rate. Among the patients who survive NHIE, 28% suffer from major neurodevelopment issues and 26% develop cerebral palsy. There are academic initiatives looking to develop treatments in this area. In addition, one intervention being investigated by the pharmaceutical industry is an IV infusion of 2-Iminobiotin. Neurophyxia B.V. attained Orphan Drug Designation for this treatment in both Europe and the United States and is conducting a Phase 2 trial.

Cannabinoid Rationale for Treating NHIE

The pathophysiology of NHIE includes processes such as apoptosis, oxidative stress, inflammation and excitotoxicity, and may involve not only the brain, but also other organs. Some cannabinoids are able to influence all of these processes, but unlike other therapeutic compounds under development, can combine these neuroprotective strategies within a single molecule. Firstly, cannabinoids can act on nuclear receptors that control neuronal homeostasis and survival. Secondly, not only do cannabinoids have important free radical scavenging actions, but they may also upregulate and activate endogenous antioxidant defenses. Thirdly, cannabinoids influence the immune network and modulate phenomena associated with infection or inflammation, via inhibition of macrophage and neutrophil migration, natural killer cell proliferation, and by their ability to inhibit harmful cytokine production. It has been widely reported that endocannabinoids are able to protect the glial cell, an effect that may be independent of CB receptors. Finally, the endocannabinoid system, or ECS, has been shown to be neuroprotective in animal models — the levels of endogenous cannabinoids become enhanced in the brains of newborn rats after acute injury, acting as a protective response, and it has been proposed that one additional mechanism by which plant cannabinoids work is by preventing the enzymatic degradation of endocannabinoids, thus enhancing endogenous defense mechanisms. Recent research into the neuroprotection that has been shown by cannabinoids in animal models of neonatal hypoxia has also suggested a role for the 5HT1A receptor, since some of the beneficial effects can be blocked by 5HT1A receptor antagonists.
CBD as the Primary Cannabinoid Product Candidate in NHIE

In addition to its other properties, the possible neuroprotective effects of CBD have been examined. These neuroprotective effects are thought to be based mainly on the potent anti-inflammatory and anti-oxidant properties of CBD, although other actions of CBD that might also account for CBD-induced neuroprotection including: inhibition of calcium transport across membranes; inhibition of anandamide uptake and enzymatic hydrolysis; inhibition of iNOS protein expression and NF-κB activation; and inhibition of adenosine uptake. In a similar fashion to endocannabinoids, adenosine is thought to be part of a natural neuroprotective system, because adenosine levels rise in response to hypoxic insult in the brain and increasing extracellular adenosine acts as a neuroprotectant. It has been demonstrated that CBD enhances adenosine signaling through the inhibition of adenosine re-uptake and therefore indirectly activates the adenosine A2A receptor. Previously, it was demonstrated that CBD reduces brain damage after ischemic injury in adult animals. In a newborn piglet model of NHIE, CBD improved brain activity as measured by an EEG and reduced the numbers of seizures by half, while histological analysis of brain tissues showed that neuron degeneration was reduced. Neurological exams showed improved neurobehavioral performance up to three days after insult. There were also significant beneficial extra cerebral effects and the dose of dopamine needed by the animals to maintain blood pressure was less than half of what was required in vehicle-treated animals.

Our NHIE Research

In a paper by Castillo et al., published in Neurobiology of Disease in 2010, reporting results from our pre-clinical collaboration, CBD protected newborn mice forebrain slices from oxygen and glucose deprivation. We have further demonstrated that CBD was neuroprotective even when administered 18 hours after the hypoxic insult. A study from our pre-clinical collaboration with Lafuente, published in Paediatric Research in 2011, showed that administration of CBD to newborn piglets at doses much lower than those reported in the literature appears to protect brain cells, preserve brain activity, prevent seizures and improve neurobehavioral performance. These neuroprotective effects were not only free from side effects in the piglets but also associated with some cardiac, hemodynamic and ventilatory benefits unlike other promising compounds with neuroprotective activity. This data supports the view of CBD as a possible therapy for asphyxiated newborns. In a paper by Pazos et al. published in Neuropharmacology in 2012, post hypoxic-ischemic administration of CBD to newborn rats was shown to reduce the volume of brain damage, restore neurobehavioral function long term and reserve myelinization. In a second paper by Pazos et al., published in Neuropathology in 2013, reporting results from our pre-clinical collaboration, post hypoxic-ischemic administration of CBD was shown, in a piglet model, to reduce necrotic and apoptotic cell death, recover brain activity, restore neurobehavioral function in the short term and enhance hypothermia protection.

Our NHIE clinical program

We held a pre-IND meeting with the FDA to discuss the development program for an intravenous CBD formulation (GWP42003) in the treatment of NHIE. In April 2015, we received Orphan Drug Designation from the FDA for CBD for the treatment of NHIE and in July 2015 we received fast track designation. In July 2015 we received Orphan Drug Designation from the EMA for CBD for the treatment of perinatal asphyxia, an alternate term that describes the same condition. We expect to commence a Phase 1 trial of GWP42003 in healthy volunteers in the fourth quarter of 2016.

Glioma

Beyond epilepsy-related orphan diseases, we are evaluating a combination product containing GWP42002:GWP42003 (THC:CBD) in the treatment of recurrent glioblastoma multiforme, or GBM, a particularly aggressive brain tumor. We have received Orphan Drug Designation from the FDA for GWP 42002:GWP42003 combination for the treatment of GBM.

Market Overview

Glioma describes any tumor that arises from the glial tissue of the brain. Glioblastoma is a particularly aggressive tumor that forms from abnormal growth of glial tissue. According to the New England Journal of Medicine, GBM accounts for approximately 46% of the 22,500 new cases of brain cancer diagnosed in the United States each year. Treatment options are limited and expected survival is a little over one year. GBM is considered a rare disease by the FDA and the EMA.
Our Research

In pre-clinical models, we have shown cannabinoids to be orally active in the treatment of gliomas and, in addition, have shown tumor response to be positively associated with tissue levels of cannabinoids. We have identified the putative mechanism of action for our cannabinoid product candidates, where autophagy and programmed cell death are stimulated via inhibition of the akt/mTORC1 axis. We have shown in in vivo studies that cannabinoids have a synergistic effect with temozolomide, the standard chemotherapeutic agent used in the treatment of glioma.

A recent study carried out in collaboration with us by specialists at St. George’s University of London, was the first to show a dramatic effect on brain tumors when combining cannabinoids with irradiation. This research, published in Molecular Cancer Therapeutics, showed that tumor growth in mouse brain was significantly slowed when a combination of THC and CBD was used with irradiation and tumor inhibition was higher than observed with irradiation alone.

In light of this promising pre-clinical research, in 2014, we commenced an early proof of concept Phase 1b/2a clinical trial in 20 patients with recurrent GBM evaluating GWP42002:GWP42003 in combination with temozolomide, the current standard of care. This trial is a two-part study with an open-label phase to assess safety and tolerability followed by a double-blind, randomized, placebo-controlled phase with patients randomized to receive active or placebo. The first phase, an open-label safety evaluation of GWP42002:GWP42003 comprising two cohorts of three patients each completing two cycles (months) of treatment is complete. Safety data from these initial patient cohorts has been assessed by the independent safety monitoring board and their approval was given to proceed into the Phase 2a placebo-controlled phase of this trial.

We have now completed recruitment of the 20 patient placebo-controlled Phase 2a part of this trial, and top-line data is expected in the fourth quarter of 2016. The primary outcome measure is 12 month progression free survival.

The principal cannabinoids we have studied in pre-clinical models of glioma are GWP42002 and GWP42003 in various ratios, and this first trial employs Sativex, which contains an equal ratio of GWP42002 and GWP42003, to establish a proof of principle. It is anticipated that subsequent development would focus on a product candidate with a different ratio of GWP42002 and GWP42003.

Other Pipeline Product Candidates

Schizophrenia

Market Overview

Schizophrenia is a chronic disease that manifests through disturbances of perception, thought, cognition, emotion, motivation and motor activity. Over a lifetime, about 1% of the population will develop schizophrenia. All anti-psychotic treatments for schizophrenia rely primarily upon their antagonistic action at the dopamine D2 receptor for their antipsychotic effect. They produce a wide range of adverse events, and are often poorly tolerated by patients resulting in poor compliance with treatment. Current antipsychotics also have little or no effect upon the “negative” symptoms (blunted mood and lack of pleasure, motivation and movement) of schizophrenia or the associated cognitive deficit. Furthermore, the “positive” symptoms (such as hallucinations, delusions and thought disorder) of at least one-third of patients fail to respond adequately to current treatments.

Our Research

GWP42003 has shown notable anti-psychotic effects in accepted pre-clinical models of schizophrenia and importantly has also demonstrated the ability to reduce the characteristic movement disorders induced by currently available anti-psychotic agents. In September 2015, we announced positive top line results from an exploratory Phase 2 placebo-controlled clinical trial of CBD in 88 patients with schizophrenia who had previously failed to respond adequately to first line anti-psychotic medications. Over a series of exploratory endpoints, CBD was consistently superior to placebo, with the most notable differences being in the PANSS positive subscale (p=0.018), the Clinical Global Impression of Severity (p=0.04) and Clinical Global Impression of Improvement (p=0.02). The proportion of responders (improvement in PANSS Total score...
greater than 20%) on CBD was higher than that of participants on placebo and the Scale for Assessment of Negative Symptoms showed a trend in favor of CBD which reached statistical significance for patients taking CBD together with one of the leading first line anti-psychotic medications. The safety profile of CBD was reassuring, with no serious adverse events and an overall frequency of adverse events very similar to placebo.

We believe that the signals of efficacy demonstrated in this trial, together with a notably reassuring safety profile, provide us with the prospect of new and distinct cannabinoid neuropsychiatric product pipeline opportunity as the mechanism of CBD does not appear to rely on the dopamine D2 receptor augmentation of standard antipsychotics. We are now analyzing the data to fully understand the appropriate next steps regarding product development in schizophrenia with future research likely focused on pediatric orphan neuropsychiatric indications. Additionally, our pre-clinical research findings suggest that a range of other psychiatric conditions may be promising targets for cannabinoid therapeutics.

**Type-2 Diabetes**

**Market Overview**

According to the American Diabetes Association, 25.8 million individuals in the United States, or 8.3% of the population, have diabetes, of which at least 90% have the type-2 form. There is no cure for diabetes, so treatments are aimed primarily at controlling blood glucose levels. There is recognition that advances in the treatment of type-2 diabetes should focus not merely on glucose control but in protecting the overworked pancreatic islet cells from failure. Thus, there is an unmet need for improved insulin sensitizer drugs and oral treatments that result in a restoration of normal insulin production and glucose-dependent release of insulin from pancreatic islets.

**Our Research**

We have completed a Phase 2a trial in the treatment of dyslipidemia in patients with type-2 diabetes. This five-arm randomized, double-blind, placebo-controlled, parallel group, pilot trial of GWP42004 (5mg), GWP42003 (100mg) and two separate ratios (5mg:5mg and 100mg:5mg) of GWP42003 and GWP42004. Each treatment was delivered in the form of oral capsules and administered twice daily. The trial enrolled a total of 62 type-2 diabetes patients, such that each treatment group had 11 to 14 patients. Although GWP42004 showed no benefit in lipid control, the trial showed that GWP42004, an oral cannabinoid treatment, produced the following desirable anti-diabetic effects: reduced fasting plasma glucose levels (p=0.04), with an increase in fasting insulin (p=0.289), and improved pancreatic beta-cell function (p=0.0074).

In March 2014, we commenced a larger placebo-controlled Phase 2 dose ranging trial of GWP42004. The primary objective of this trial is to compare the change in glycemic control in patients with type-2 diabetes when treated with one of three doses of GWP42004 or placebo as add-on therapy, to metformin with the primary endpoint being change from baseline to the end of treatment in mean glycosylated hemoglobin A1c (HbA1c) level. The safety and tolerability of GWP42004 compared with placebo will also be assessed.

This trial is now completed and a preliminary analysis of the topline data shows that this trial did not meet its primary endpoint. The drug was well tolerated with no serious adverse events. We are undertaking further evaluation of the data to determine whether to pursue further development of GWP42004 within the field of type-2 diabetes.

**Sativex for Cancer Pain**

Sativex, or nabiximols, is an oromucosal spray consisting of a formulated extract of the cannabis sativa plant that contains the principal cannabinoids delta-9-tetrahydrocannabinol, or THC, and CBD. We have been evaluating Sativex in a Phase 3 program to treat persistent pain in people with advanced cancer who experience inadequate pain relief from optimized chronic opioid therapy, the current standard of care. The costs of the Phase 3 cancer pain program have been fully funded by Otsuka Pharmaceutical Co. Ltd, or Otsuka, who hold exclusive rights to commercialize Sativex in the United States.

This Phase 3 program consisted of three pivotal Phase 3 trials. Although Sativex did not meet the primary endpoint in these trials, a pre-specified subgroup analysis of U.S. patients across the Phase 3 trials showed a statistically significant improvement for Sativex compared to placebo (n=248, p=0.02). GW Pharma
and Otsuka have consulted with the FDA and received feedback that this analysis of U.S. patients would not be deemed pivotal. GW Pharma and Otsuka expect to meet to discuss whether there are any next steps for Sativex in the United States within the scope of this partnership.

Sativex for Cerebral Palsy in Children

We are currently conducting a Phase 2 clinical trial of Sativex to assess the efficacy, safety and tolerability of Sativex as an adjunctive treatment to existing anti-spasticity medications in children aged 8 to 18 years with spasticity due to cerebral palsy or traumatic central nervous system injury who have not responded adequately to existing anti-spasticity medications. This trial is a randomized, double-blind, placebo-controlled trial followed by a 24-week open label extension phase and is expected to enroll approximately 70 patients and we expect to report data from this trial in the fourth quarter of 2016.

Pre-clinical developments

In addition to our extensive in-house research organization, we have established a global network of leading scientists in the cannabinoid field. Our proprietary cannabinoid product platform allows us to discover, develop and commercialize additional novel first-in-class cannabinoid products across a broad range of therapeutic areas. Some of the more advanced programs include:

- The use of CBD and other cannabinoid candidates in Duchenne muscular dystrophy (DMD), the most common inherited lethal childhood orphan disease in the world, where new discoveries lead researchers to conclude that muscle cells respond positively to CBD by increasing metabolic output and improving mitochondrial function.
- In Glioma, cannabinoids induce glioma stem-like cell differentiation and inhibit gliomagenesis and research suggests that a combination of cannabinoids with other anticancer agents can eliminate GICs (Glioma Initiating Cells) which can cause recurrence of tumors after surgery. These findings are significant as GICs are resistant to most anticancer therapies and therefore reduce the apparent effectiveness of conventional brain cancer therapies.
- In various other cancers including ovarian and pancreatic cancer, pre-clinical research has shown that cannabinoids can act in concert with current cancer treatments such as chemotherapy and radiotherapy to enhance therapeutic response in animal models.
- The use of the cannabinoid CBG in the treatment of chemotherapy-induced cachexia where pre-clinical data supports a multimodal action that includes a protective effect on overall loss of muscle mass, stimulation of feeding, and a normalized metabolic profile.

Our Commercialized Product: Sativex® for MS Spasticity

Sativex is an oromucosal spray of a formulated extract of the cannabis sativa plant that contains the principal cannabinoids THC and CBD as well as specific minor cannabinoids and other non-cannabinoid components. We developed Sativex to be administered as an oral spray, whereby the active ingredients are absorbed in the lining of the mouth, either under the tongue or inside the cheek. The product has been granted the U.S. Adopted Name, or USAN, of nabiximols.

Our licensing partners are commercializing Sativex for MS spasticity in 16 countries outside the United States. We have also received regulatory approval in an additional 12 countries, and we anticipate commercial launches in several of these countries in the next 12 months. Two additional countries have recommended approval for Sativex and regulatory filings are ongoing in 12 other countries, principally in the Middle East and Latin America where we expect approvals over the next 12 months.

MS Spasticity Indication in the United States

We previously opened an IND with the FDA for the MS spasticity indication and this has now been withdrawn.

Our Strategic Partnerships

To support the development and commercialization of Sativex, we have entered into license and development agreements with the following major pharmaceutical companies: Otsuka in the United States;
Almirall S.A., or Almirall, in Europe (excluding the United Kingdom) and Mexico; Novartis Pharma AG, or Novartis, in Australia and New Zealand, Asia (excluding Japan, China and Hong Kong), the Middle East (excluding Israel) and Africa; Bayer HealthCare AG, or Bayer, in the United Kingdom and Canada; Ipsen Biopharm Ltd, or Ipsen, in Latin America (excluding Mexico and the Islands of the Caribbean); and Neopharm Group, or Neopharm, in Israel. These agreements provide our collaborators with the sole right to commercialize Sativex in exclusive territories for all indications. From our incorporation through March 31, 2016, these agreements have yielded cash of £67.8 million in upfront fees and milestone payments. We are entitled to receive additional lump sum payments upon the achievement of certain regulatory and commercial milestones in the future, but are not relying on any of these milestones being achieved. Upon commercialization, we are also entitled to receive revenue from the supply of products as well as royalties on product sales. In addition, under the terms of our agreement with Otsuka, all pre-clinical and clinical costs associated with the development of Sativex in the United States are fully funded by Otsuka.

Following the failure of the Sativex cancer pain trials, GW Pharma and Otsuka expect to meet to discuss whether there are any next steps for Sativex in the United States within the scope of this partnership.

With the exception of Sativex, we retain global commercial rights to all of our other product pipeline candidates.

**Our Strengths**

We believe that we offer the following key distinguishing characteristics:

- **A late stage product, Epidiolex, in pediatric epilepsy for which we have generated positive Phase 3 data.** We have reported positive Phase 3 data for Epidiolex in both Dravet syndrome and LGS. Each of these conditions is a severe, infantile-onset, genetic, drug-resistant epilepsy syndrome for which we have secured Orphan Drug Designation from the FDA. We expect to engage with FDA regarding our filing approach early in the third quarter of 2016 and submit an NDA to the FDA in the first half of 2017.

- **Additional indications for Epidiolex to expand epilepsy market opportunity.** We believe that there is potential for the development of Epidiolex in additional rare childhood-onset epilepsy indications. Physician reported data on patients receiving Epidiolex under physician-led INDs includes promising signals of clinical effect in patients with conditions other than Dravet syndrome and LGS. One of these additional indications is TSC, and we commenced Phase 3 development in this indication in April 2016. Another is IS, and we expect to commence clinical development in the IS indication in the fourth quarter of 2016, and there are additional potential target indications under consideration for future development.

- **We retain global commercial rights to Epidiolex and believe it has significant market potential.** We are building a U.S. commercial organization led by Julian Gangolli as President, North America, who joined us in June 2015 having previously held the same position at Allergan. We have also recruited U.S. medical affairs, clinical trials and commercial staff, many of whom have strong epilepsy knowledge and experience. There is a significant unmet need within the field of epilepsy and we believe that U.S. physician awareness and enthusiasm for Epidiolex is high.

- **Commercialized product validates development and regulatory pathway.** We believe that the successful development and regulatory approval of Sativex in MS spasticity outside the United States provides important validation of our proprietary cannabinoid product platform. On this basis, we believe that we can develop a portfolio of additional cannabinoid therapeutics.

- **Additional pipeline programs within epilepsy, autism, and pediatric neurology.** We are in Phase 2 clinical development for an additional product candidate, GWP42006 (CBDV), in adult epilepsy patients. GWP42006 has also shown promising pre-clinical data within the field of ASDs and we expect to commence Phase 2 development in this therapeutic area in the first half of 2017. In addition, we have received Orphan Drug Designation from the FDA for CBD in the treatment of NHIE and plan to commence Phase 1 development of an intravenous CBD formulation in the treatment of NHIE in the fourth quarter of 2016.
• A pipeline of additional cannabinoid orphan and non-orphan drug opportunities for which we retain global commercial rights. We are conducting a Phase 1b/2a trial of another product, our combination GWP42002:GWP42003, to treat GBM. We have successfully completed a Phase 2 trial in schizophrenia for our product candidate, GWP42003.

• Opportunity for first-in-class treatments across a large number of therapeutic targets. We are at the forefront of the commercialization of cannabinoid therapeutics using our proprietary product platform to identify, validate and develop innovative first-in-class therapeutics that are designed to meet significant unmet medical needs.

• Strong competitive position in a highly specialized and regulated field. We believe that we are uniquely positioned to benefit from the significant potential within the field of cannabinoid therapeutics in which we have developed a successful track record and expertise, as well as an intellectual property portfolio, during our 18 years of operations.

• In-house manufacturing capabilities and expertise in controlled substances. We operate under Good Manufacturing Practice commercial manufacturing licenses in the United Kingdom, which give us the capability to supply our products to global markets. We have successfully exported cannabinoid commercial or research materials to 37 countries and have substantial expertise in relevant international and national regulations in relation to the research, distribution and commercialization of cannabinoid therapeutics.

• Highly experienced management team and network of leading scientists. Several members of our leadership team have been in place for over ten years. We have a fully integrated in-house research and development organization, regulatory capabilities and commercial manufacturing expertise. We closely collaborate with a broad network of leading scientists in the cannabinoid field.

Our Business Strategy

Our goal is to capitalize on our leading position in the field of plant-derived cannabinoid therapeutics by pursuing the following strategies:

• Secure regulatory approval and launch using our own commercial organization our lead product candidate Epidiolex in Dravet syndrome and LGS in the United States and around the world. We have reported positive Phase 3 data in Dravet syndrome and LGS and expect to engage with FDA in the third quarter of 2016 regarding our filing approach and submit a NDA to the FDA in the first half of 2017. We also expect to submit regulatory applications in Europe and elsewhere around the world. We are building U.S. and European commercial organizations in preparation for potential launch of Epidiolex.

• Expand the market opportunity for Epidiolex within the field of epilepsy. We have commenced Phase 3 clinical development of Epidiolex for TSC and expect to commence clinical development of Epidiolex for IS in the fourth quarter of 2016. We are evaluating additional indications for Epidiolex within the field of epilepsy.

• Develop additional product candidates within the field of epilepsy and pediatric neurology. We have a second product candidate, GWP42006, for which a Phase 2 clinical trial in epilepsy is underway with data expected in the first quarter of 2017. We expect to commence Phase 2 development of GWP42006 in the field of ASD in the first half of 2017. We also expect to commence a Phase 1 clinical trial in 2016 for an intravenous CBD formulation in the treatment of NHIE. In addition, following positive proof-of-concept data in a Phase 2 schizophrenia trial, we expect to conduct further research within the field of psychiatric disease in children. We retain global commercial rights to these programs.

• Leverage our proprietary cannabinoid product platform to discover, develop and commercialize additional novel first-in-class cannabinoid products. We believe our established platform, including our in-house development expertise, allows us to achieve candidate selection and proof-of-concept in an efficient manner.
Further strengthen our competitive position. We will continue to develop our extensive international network of the most prominent scientists in the cannabinoid field and secure additional intellectual property rights.

Government Regulation and Product Approval

Expanded Access to Investigational Drugs

An investigational drug may be eligible for clinical use outside the context of a manufacturer-sponsored clinical trial of the drug. “Expanded access” refers to the use of an investigational drug where the primary purpose is to diagnose, monitor, or treat a patient’s disease or condition rather than to collect information about the safety or effectiveness of a drug. Expanded access INDs are typically sponsored by individual physicians to treat patients who fall into one of three FDA-recognized categories of expanded access: expanded access for individual patients, including for emergency use; expanded access for intermediate-size patient populations; and expanded access for large patient populations under a treatment IND or treatment protocol. For all types of expanded access, FDA must determine prior to authorizing expanded access that: (1) the patient or patients to be treated have a serious or life-threatening disease or condition and there is no comparable or satisfactory alternative therapy; (2) the potential patient benefit justifies the potential risks of use and that the potential risks are not unreasonable in the context of the disease or condition to be treated; and (3) granting the expanded access will not interfere with the initiation, conduct, or completion of clinical studies in support of the drug’s approval. In addition, the sponsor of an expanded access IND must submit IND safety reports and, in the cases of protocols continuing for one year or longer, annual reports to the FDA. Expanded access programs are not intended to yield information relevant to evaluating a drug’s effectiveness for regulatory purposes.

Controlled Substance Rescheduling

Following NDA approval of a drug containing a Schedule I controlled substance, that substance must be rescheduled as a Schedule II, III, IV or V substance before it can be marketed. On November 17, 2015, H.R. 639, Improving Regulatory Transparency for New Medical Therapies Act, passed through both houses of Congress and on November 25, 2015 the Bill was signed into law. The new law removes uncertainty associated with timing of the DEA rescheduling process after NDA approval. Specifically, it requires DEA to issue an “interim final rule,” pursuant to which a manufacturer may market its product no later than 90 days after the later of: (1) the date on which DEA receives from FDA the scientific and medical evaluation and scheduling recommendation; or (2) the date on which DEA receives from FDA notification that FDA has approved the drug. The new law also preserves the period of orphan marketing exclusivity for the full seven years such that this period only begins with the approval of the NDA or DEA scheduling, whichever is later. This contrasts with the previous situation whereby the orphan “clock” began to tick upon FDA approval, even though the product could not be marketed until DEA scheduling was complete.
RISK FACTORS

Risks Related to Our Business

We are dependent on the success of our product candidates, none of which may receive regulatory approval or be successfully commercialized.

Our success will depend on our ability to successfully commercialize our product pipeline, including commercialization of Epidiolex and our other cannabinoid product candidates. We are evaluating Epidiolex for the treatment of Dravet syndrome, LGS and TSC in the United States and have initiated Phase 3 trials for these indications. Nevertheless, Epidiolex may never receive U.S. regulatory approval for the treatment of any of these indications. Even if completed Phase 3 clinical trials and/or Phase 3 clinical trials conducted for U.S. approval show positive results, there can be no assurance that the FDA will approve Epidiolex or any other product candidate for any given indication for several potential reasons, including failure to follow Good Clinical Practice, or GCP, negative assessment of risk to benefit, unacceptable risk of abuse or diversion, insufficient product quality control and standardization, non-GMP compliant manufacturing facilities and in the absence of a protocol agreed through the FDA’s Special Protocol Assessment process, refusal by FDA to accept our clinical trial design/or failure to agree on appropriate clinical endpoints.

Our ability to successfully commercialize Epidiolex, if approved, Sativex and our other product candidates will depend on, among other things, our ability to:

• successfully complete pre-clinical studies and clinical trials, including human factors testing requirements and the assessment of abuse potential;
• demonstrate to the FDA and similar foreign regulatory authorities that efficacy of Epidiolex, Sativex or any other product candidates in clinical trials, can be attributed to the investigative product and not exclusively to its interaction with concomitant medications;
• receive regulatory approvals from the FDA and similar foreign regulatory authorities;
• produce, through a validated process, in manufacturing facilities inspected and approved by regulatory authorities, including the FDA, sufficiently large quantities of the product candidate, and the related Botanical Drug Substances, or BDSs, to permit successful commercialization;
• build and maintain strong sales, distribution and marketing capabilities sufficient to launch commercial sales of our product candidates, or otherwise establish collaborations with third parties for the commercialization of our product candidates;
• obtain reimbursement from payers such as government health care programs and insurance companies and other private payers, as well as achieve commercially attractive levels of pricing;
• secure acceptance of our product candidates from physicians, health care payers, patients and the medical community;
• create positive publicity surrounding our product candidates;
• manage our spending as costs and expenses increase due to clinical trials and commercialization; and
• obtain and enforce sufficient intellectual property for our product candidates.

Our failure or delay with respect to any of the factors above could have a material adverse effect on our business, results of operations and financial condition.

Our product candidates, if approved, may be unable to achieve the expected market acceptance and, consequently, limit our ability to generate revenue from new products.

Even when product development is successful and regulatory approval has been obtained, our ability to generate significant revenue depends on the acceptance of our products by physicians and patients. We cannot assure you that Epidiolex or our other product candidates will achieve the expected market acceptance and revenue if and when they obtain the requisite regulatory approvals. The market acceptance of any product...
depends on a number of factors, including the indication statement and warnings approved by regulatory authorities in the product label, continued demonstration of efficacy and safety in commercial use, physicians’ willingness to prescribe the product, reimbursement from third-party payers such as government health care systems and insurance companies, the price of the product, the nature of any post-approval risk management plans mandated by regulatory authorities, competition, and marketing and distribution support. Any factors preventing or limiting the market acceptance of our products could have a material adverse effect on our business, results of operations and financial condition.

In respect of our product candidates targeting rare indications, orphan drug exclusivity may afford limited protection, and if another party obtains orphan drug exclusivity for the drugs and indications we are targeting, we may be precluded from commercializing our product candidates in those indications during that period of exclusivity.

The first New Drug Application, or NDA, applicant with an Orphan Drug Designation for a particular active moiety to treat a specific disease or condition that receives FDA approval is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. There is no assurance that we will successfully obtain Orphan Drug Designation for future rare indications or orphan exclusivity upon approval of any of our product candidates that have already obtained Orphan Drug Designation. Even if we do obtain orphan exclusivity for any product candidate, the exclusive marketing rights may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug. Moreover, a drug product with an active moiety that is a different cannabinoid from that in our drug candidate or, under limited circumstances, the same drug product, may be approved by the FDA for the same indication during the period of marketing exclusivity. The limited circumstances include a showing that the second drug is clinically superior to the drug with marketing exclusivity through a demonstration of superior safety or efficacy or that it makes a major contribution to patient care. In addition, if a competitor obtains approval and marketing exclusivity for a drug product with an active moiety that is the same as that in a product candidate we are pursuing for the same indication, approval of our product candidate would be blocked during the period of marketing exclusivity unless we could demonstrate that our product candidate is clinically superior to the approved product. In addition, if a competitor obtains approval and marketing exclusivity for a drug product with an active moiety that is the same as that in a product candidate we are pursuing for a different orphan indication, this may negatively impact the market opportunity for our product candidate. There have been legal challenges to aspects of the FDA’s regulations and policies concerning the exclusivity provisions of the Orphan Drug Act, and future challenges could lead to changes that affect the protections afforded our products in ways that are difficult to predict. In a recent successful legal challenge, a court invalidated the FDA’s denial of orphan exclusivity to a drug on the grounds that the drug was not proven to be clinically superior to a previously approved product containing the same ingredient for the same orphan use. In response to the decision, the FDA released a policy statement stating that the court’s decision is limited just to the facts of that particular case and that the FDA will continue to require the sponsor of a designated drug that is the “same” as a previously approved drug to demonstrate that its drug is clinically superior to that drug upon approval in order to be eligible for orphan drug exclusivity, or in some cases, to even be eligible for marketing approval. In the future, there is the potential for additional legal challenges to the FDA’s orphan drug regulations and policies, and it is uncertain how such challenges might affect our business.

In the European Union, if a marketing authorization is granted for a medicinal product that is designated an orphan drug, that product is entitled to ten years of marketing exclusivity. During the period of marketing exclusivity, no similar medicinal product may be granted a marketing authorization for the orphan indication. There is no assurance that we will successfully obtain Orphan Drug Designation for future rare indications or orphan exclusivity upon approval of any of our product candidates that have already obtained designation. Even if we obtain orphan exclusivity for any product candidate, the exclusivity period can be reduced to six years if at the end of the fifth year it is established that the orphan designation criteria are no longer met or if it is demonstrated that the orphan drug is sufficiently profitable that market exclusivity is no longer justified. Further, a similar medicinal product may be granted a marketing authorization for the same indication notwithstanding our marketing exclusivity if we are unable to supply sufficient quantities of our product, or if the second product is safer, more effective or otherwise clinically superior to our orphan drug. In addition, if a competitor such as Insys Therapeutics Inc. obtains marketing authorization and orphan

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exclusivity for a product that is similar to a product candidate we are pursuing for the same indication, approval of our product candidate would be blocked during the period of orphan marketing exclusivity unless we could demonstrate that our product candidate is safer, more effective or otherwise clinically superior to the approved product.

**We have to date commercialized only one product, Sativex.**

Our only approved product, Sativex is currently being commercialized for spasticity due to multiple sclerosis, or MS, outside the United States. Even if we obtain regulatory approval for a product other than Sativex, our future success will still depend in part on the continued successful commercialization of Sativex. Although Sativex is currently approved in 28 countries outside of the United States for MS spasticity, and is sold in 16 of those countries, it may never be successfully commercialized in all of these jurisdictions. The commercial success of Sativex for MS spasticity depends on a number of factors beyond our control, including the willingness of physicians to prescribe Sativex to patients, payers’ willingness and ability to pay for the drug, the level of pricing achieved, patients’ response to Sativex, the ability of our marketing partners to generate sales and, given that we generate revenue from the supply of Sativex to our partners at a fixed percentage of partners’ net sales and that any increase in our manufacturing costs will adversely affect our margins and our financial condition, our ability to manufacture Sativex on a cost effective and efficient basis. Accordingly, we cannot assure you that we will succeed in generating revenue growth through the commercialization of Sativex for MS spasticity. If we are not successful in the continued commercialization of Sativex for MS spasticity, our business, results of operations and financial condition may be harmed.

**We expect to face intense competition, often from companies with greater resources and experience than we have.**

The pharmaceutical industry is highly competitive and subject to rapid change. The industry continues to expand and evolve as an increasing number of competitors and potential competitors enter the market. Many of these competitors and potential competitors have substantially greater financial, technological, managerial and research and development resources and experience than we have. Some of these competitors and potential competitors have more experience than we have in the development of pharmaceutical products, including validation procedures and regulatory matters. In addition, Sativex competes with, and our product candidates, if successfully developed, will compete with, product offerings from large and well-established companies that have greater marketing and sales experience and capabilities than we or our collaboration partners have. In particular, Insys Therapeutics, Inc. has publicly stated its intention to develop cannabidiol (CBD) in Dravet syndrome, LGS, Infantile Spasms, glioma and potentially other indications. Zogenix, Inc. is developing low dose fenfluramine in Dravet syndrome and has commenced an open-label study with this product in LGS, and other companies with greater resources than us may announce similar plans in the future. In addition, there are non-FDA approved CBD preparations being made available from companies in the medical marijuana industry, which may be competitive to Epidiolex. If we are unable to compete successfully, our commercial opportunities will be reduced and our business, results of operations and financial conditions may be materially harmed.

**Product shipment delays could have a material adverse effect on our business, results of operations and financial condition.**

The shipment, import and export of Epidiolex, Sativex and our other product candidates require import and export licenses. In the United States, the FDA, U.S. Customs and Border Protection, and the Drug Enforcement Administration, or DEA, and in the United Kingdom, the Home Office, and in other countries, similar regulatory authorities regulate the import and export of pharmaceutical products that contain controlled substances, including Sativex, Epidiolex and our other product candidates. Specifically, the import and export process requires the issuance of import and export licenses by the relevant controlled substance authority in both the importing and exporting country. We may not be granted, or if granted, maintain, such licenses from the authorities in certain countries. Even if we obtain the relevant licenses, shipments of Sativex, Epidiolex and our product candidates may be held up in transit, which could cause significant delays and may lead to product batches being stored outside required temperature ranges. Inappropriate storage may damage the product shipment resulting in a partial or total loss of revenue from one or more shipment of Sativex.
Epidiolex or our other product candidates. A partial or total loss of revenue from one or more shipment of Sativex, Epidiolex or our other product candidates could have a material adverse effect on our business, results of operations and financial condition.

If the price for Sativex or any future approved products decreases or if governmental and other third-party payers do not provide adequate coverage and reimbursement levels, our revenue and prospects for profitability will suffer.

Reimbursement systems in international markets vary significantly by country and by region, and reimbursement approvals generally must be obtained on a country-by-country basis. Where we have chosen to collaborate with a third party on product candidate development and commercialization, our partner may elect to reduce the price of our products in order to increase the likelihood of obtaining reimbursement approvals. In many countries, products cannot be commercially launched until reimbursement is approved and the negotiation process in some countries can exceed 12 months. In addition, pricing and reimbursement decisions in certain countries can be affected by decisions taken in other countries, which can lead to mandatory price reductions and/or additional reimbursement restrictions across a number of other countries, which may thereby adversely affect our sales and profitability. In the event that countries impose prices that are not sufficient to allow us or our partners to generate a profit, our partners may refuse to launch the product in such countries or withdraw the product from the market, which would adversely affect sales and profitability. For example, whereas the All Wales Medicines Strategy Group has recommended Sativex for use in MS spasticity in Wales, the National Institute for Clinical Excellence published MS treatment guidelines which did not recommend Sativex for use in England. In Italy the government approves an annual quota for purchasing hospital medicines from each pharmaceutical company. If the public spending on a pharmaceutical company’s hospital medicines breaks the approved annual quota, the pharmaceutical company has to pay back 50% of the payments it has received for having sold medicines to public hospitals in excess of their approved annual quota. This has caused us to commence discussions with our partner, Almirall, in order to ascertain how any reimbursement to the Italian government will be allocated between the parties so as to maintain a level of profitability for us on our sales of Sativex in Italy and has also caused us to commence legal proceedings in Italy to challenge the quota levied on Sativex hospital sales by the Italian government. While this example refers to the commercialization of Sativex, the same or similar events, such as price decreases, government mandated rebates or unfavorable reimbursement decisions, could affect the pricing and reimbursement of Epidiolex and our other product candidates and could have a material adverse effect on our business, results of operations and financial condition.

Problems in our manufacturing process, failure to comply with manufacturing regulations or unexpected increases in our manufacturing costs could harm our business, results of operations and financial condition.

We are responsible for the manufacture and supply of Sativex to our collaboration partners and for the manufacture and supply of Sativex, Epidiolex and other product candidates for use in clinical trials. The manufacturing of Sativex and our product candidates necessitates compliance with Good Manufacturing Practice, or GMP, and other regulatory requirements in jurisdictions internationally. Our ability to successfully manufacture Sativex, Epidiolex and other product candidates involves cultivation of botanical raw material from specific cannabinoid plants, extraction and purification processes, manufacture of finished products and labeling and packaging, which includes product information, tamper evidence and anti-counterfeit features, under tightly controlled processes and procedures. For Sativex and certain of our product candidates, production also requires the cultivation of cannabinoid plants under highly controlled and standardized conditions. In addition, we must ensure chemical consistency among our batches, including clinical batches and, if approved, marketing batches. Demonstrating such consistency may require typical manufacturing controls as well as clinical data. We must also ensure that our batches conform to complex release specifications. For each step in the manufacturing process for Sativex, we are currently reliant on single manufacturing facilities and no back-up facilities are yet in place. We have a second site at which we can grow the specific cannabinoid plants which produce the CBD used in Epidiolex, but we are currently reliant on a single manufacturing facility, and no back-up facilities are yet in place, for the later steps in the Epidiolex production process. Because Sativex is a complex mixture manufactured from plant materials, and because the release specifications may not be identical in all countries, certain batches may fail release testing.
and not be able to be commercialized. A number of our product candidates (excluding Epidiolex) also consist of a complex mixture manufactured from plant materials, and are therefore subject to a similar risk. If we are unable to manufacture Sativex, Epidiolex or other product candidates in accordance with regulatory specifications, including good manufacturing practices or if there are disruptions in our manufacturing process due to damage, loss or otherwise, or failure to pass regulatory inspections of our manufacturing facilities, we may not be able to meet current demand or supply sufficient product for use in clinical trials, and this may also harm our ability to commercialize Sativex, Epidiolex and our product candidates on a timely or cost-competitive basis, if at all. We are in the process of expanding and upgrading parts of our growing and manufacturing facilities in order to be able to submit an NDA for Epidiolex which would provide sufficient quantities to meet initial demand, and to meet FDA’s stringent requirements for demonstrating equivalence of the scaled up manufacturing process, a program which requires significant time and resources and which may not be successful. We are planning a significant expansion of our growing facilities over the next few years in order to meet potential peak demand for Epidiolex, including working with several new contractors and adopting new methods in order to handle and process bulk quantities of botanical raw material. We are planning to increase the scale in which we manufacture Epidiolex over the next few years in order to meet potential peak demand for Epidiolex, including working with several new contractors and, potentially, adopting new processes. These activities may be unsuccessful, may lead to delays, interruptions to supply, or may prove to be more costly than anticipated. We may fail to expand our growing and manufacturing capability in time to meet market demand for our products and product candidates. Any problems in our growing or manufacturing process could have a material adverse effect on our business, results of operations and financial condition.

In addition, before we can begin commercial manufacture of any product candidates for sale in the United States, we must obtain FDA regulatory approval for the product, which requires a successful FDA inspection of our manufacturing facilities, processes and quality systems in addition to other product-related approvals. Further, pharmaceutical manufacturing facilities are continuously subject to inspection by the FDA and foreign regulatory authorities, before and after product approval. Due to the complexity of the processes used to manufacture our product candidates, we may be unable to initially or continue to pass federal, state or international regulatory inspections in a cost effective manner. If we are unable to comply with manufacturing regulations, we may be subject to fines, unanticipated compliance expenses, recall or seizure of any approved products, total or partial suspension of production and/or enforcement actions, including injunctions, and criminal or civil prosecution. These possible sanctions would adversely affect our business, results of operations and financial condition.

Further, the processes we use for cultivation of botanical raw material and the production of product candidates for use in clinical trials may be different to the processes we use to produce commercial product and/or may not be capable of producing sufficient quantities of product for commercial purposes. We may therefore need to undertake additional manufacturing process development and scale-up activities before we can commercialize a product. This may include the conduct of bioequivalence studies to demonstrate that product produced by the process used to manufacture on a commercial scale is the same as the material used in clinical trials. If we cannot demonstrate that our commercial scale product is the same as material used in our clinical trials, we may not be permitted to sell that product, which could have an impact on our business, results of operations and financial condition.

Product recalls or inventory losses caused by unforeseen events, cold chain interruption and testing difficulties may adversely affect our operating results and financial condition.

Sativex and our product candidates are manufactured and distributed using technically complex processes requiring specialized facilities, highly specific raw materials and other production constraints. The complexity of these processes, as well as strict company and government standards for the manufacture of our products, subjects us to production risks. For example, during the manufacturing process we have from time to time experienced defects in components which have caused vial sealing faults, resulting in vial leakage, pump dispenser faults which have resulted in under-filling of vials and misalignment of labels and tamper evident seals, as well as receipt of faulty electronic dose counters from our supplier. While product batches released for use in clinical trials or for commercialization undergo sample testing, some defects may only be identified following product release. In addition, process deviations or unanticipated effects of approved process changes
may result in these intermediate products not complying with stability requirements or specifications. Some of our products must be stored and transported at temperatures within a certain range, which is known as “strict cold chain” storage and transportation. If these environmental conditions deviate, our products’ remaining shelf-lives could be impaired or their efficacy and safety could become adversely affected, making them no longer suitable for use. The occurrence or suspected occurrence of production and distribution difficulties can lead to lost inventories, and in some cases product recalls, with consequential reputational damage and the risk of product liability. The investigation and remediation of any identified problems can cause production delays, substantial expense, lost sales and delays of new product launches.

**Sativex and our product candidates contain controlled substances, the use of which may generate public controversy.**

Since Sativex, Epidiolex and our other product candidates contain controlled substances, their regulatory approval may generate public controversy. Political and social pressures and adverse publicity could lead to delays in approval of, and increased expenses for, Sativex and our product candidates. These pressures could also limit or restrict the introduction and marketing of Sativex and our product candidates. Adverse publicity from cannabis misuse or adverse side effects from cannabis or other cannabinoid products may adversely affect the commercial success or market penetration achievable by Sativex and our product candidates. The nature of our business attracts a high level of public and media interest, and in the event of any resultant adverse publicity, our reputation may be harmed.

**Business interruptions could delay us in the process of developing our product candidates and could disrupt our product sales.**

Loss of our manufacturing facilities, our growing plants, stored inventory or laboratory facilities through fire, theft or other causes, or loss of our botanical raw material due to pathogenic infection or other causes, could have an adverse effect on our ability to meet demand for Sativex, to continue product development activities and to conduct our business. Failure to supply our partners with commercial product may lead to adverse consequences, including the right of partners to take over responsibility for product supply. We currently have insurance coverage to compensate us for such business interruptions; however, such coverage may prove insufficient to fully compensate us for the damage to our business resulting from any significant property or casualty loss to our inventory or facilities.

**We have significant and increasing liquidity needs and may require additional funding.**

Our operations have consumed substantial amounts of cash since inception. For the year ended September 30, 2014, we reported a net operating cash outflow of £12.6 million and a net cash outflow from investing activities of £7.1 million. For the year ended September 30, 2015, we reported a net operating cash outflow of £46.5 million and a net cash outflow from investing activities of £17.8 million.

For the six months ended March 31, 2016, we reported a net operating cash outflow of £46.4 million and a net cash outflow from investing activities of £4.6 million.

Research and development, management and administrative expenses and cash used for operations will continue to be significant and may increase substantially in future connection with new research and development initiatives, continued product commercialization efforts and as we prepare for the potential commercial launch of Epidiolex and continue to grow as a U.S. public company. We may need to raise additional capital to fund our operations, continue to conduct clinical trials to support potential regulatory approval of marketing applications, and to fund commercialization of our products.
The amount and timing of our future funding requirements will depend on many factors, including, but not limited to:

- the timing of FDA approval, if any, and approvals in international markets of our product candidates, if at all;
- the timing and amount of revenue from sales of Sativex, or revenue from grants or other sources;
- the rate of progress and cost of our clinical trials and other product development programs;
- costs of establishing or outsourcing sales, marketing and distribution capabilities;
- costs and timing of completion of expanded in-house manufacturing facilities as well as any outsourced growing and commercial manufacturing supply arrangements for our product candidates;
- costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights associated with our product candidates;
- costs of operating as a U.S. public company;
- the effect of competing technological and market developments;
- personnel, facilities and equipment requirements; and
- the terms and timing of any additional collaborative, licensing, co-promotion or other arrangements that we may establish.

While we expect to fund our future capital requirements from a number of sources including cash flow from operations, the proceeds from further public offerings, the proceeds from the exercise of share options, we cannot assure you that any of these funding sources will be available to us on favorable terms, or at all. Further, even if we can raise funds from all of the above sources, the amounts raised may not be sufficient to meet our future capital requirements.

We identified a material weakness in our internal control over financial reporting for the fiscal year ended September 30, 2015. If we do not remediate this material weakness or are unable to implement and maintain effective internal control over financial reporting in the future, the accuracy and timeliness of our financial reporting may be adversely affected.

As required by Section 404(a) of the Sarbanes-Oxley Act, our management assessed the effectiveness of our internal control over financial reporting as of September 30, 2015. Based on its evaluation, our management concluded that due to the material weakness described below, our internal control over financial reporting was not effective as of September 30, 2015. As required by Section 404(b) of the Sarbanes-Oxley Act, our independent registered public accounting firm attested to and reported on our management’s assessment and similarly concluded that our internal control over financial reporting was not effective as of September 30, 2015. A material weakness (within the meaning of PCAOB Auditing Standard No. 5) is a deficiency, or a combination of deficiencies, in internal controls over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis.

Our management’s assessment identified one material weakness related to the controls over the accounting for the completeness and valuation of clinical trial accruals. The material weakness relates to trade and other payables on our consolidated balance sheet and research and development expenditure within our consolidated income statement. As of September 30, 2015, the date on which our management assessed our internal controls, we had not established sufficiently precise controls over the completeness and accuracy of the calculation of clinical trial accruals. During the preparation of our 2015 year-end accruals, the clinical trial accruals were not complete due to the incorrect allocation of expenditure to clinical studies, which resulted in various accounting errors related to the valuation of clinical trial accruals. We consider that these errors arose due to deficiencies in the design of our controls over the completeness and accuracy of clinical study budgets and costs incurred to date. In addition, as of September 30, 2015, the date on which our management assessed our internal controls, we had not established a sufficiently precise control to ensure completeness of clinical trial accruals in connection with progress payment liabilities. During the preparation of our 2015 year-end accruals for progress payments linked to research and development sub-contracts, our control over the review...
of contracts to identify liabilities at year-end failed to identify progress payments due under the contracts as a result of reaching certain milestones within the trial. This led to an immaterial error which was corrected following additional procedures carried out to ensure the completeness of such accruals and prior to the publication of our annual report for the year ended September 30, 2015. We consider that the error could have been material and that changes to the design of the control are required to ensure correct operation of the control in future.

Although we are working to remediate the material weakness described above and we plan to take additional steps to remediate the underlying causes thereof, our initiatives may not prove to be successful. We may also discover future deficiencies in our internal controls over financial reporting, including those identified through testing conducted by us or subsequent testing by our independent registered public accounting firm. If we are unable to achieve effective internal control over financial reporting, or if our independent registered public accounting firm determines we continue to have a material weakness in our internal control over financial reporting, we could lose investor confidence in the accuracy and completeness of our financial reports and the market price of our ordinary shares and ADSs could decline.

We are exposed to risks related to currency exchange rates.

We conduct a significant portion of our operations outside the United Kingdom. Because our financial statements are presented in pounds sterling, changes in currency exchange rates have had and could have a significant effect on our operating results. Exchange rate fluctuations between local currencies and the pound sterling create risk in several ways, including the following: weakening of the pound sterling may increase the pound sterling cost of overseas research and development expenses and the cost of sourced product components outside the United Kingdom; strengthening of the pound sterling may decrease the value of our revenues denominated in other currencies; the exchange rates on non-sterling transactions and cash deposits can distort our financial results; and commercial Sativex pricing and profit margins are affected by currency fluctuations.

If product liability lawsuits are successfully brought against us, we will incur substantial liabilities and may be required to limit the commercialization of Sativex and our product candidates.

Although we have never had any product liability claims or lawsuits brought against us, we face potential product liability exposure related to the testing of our product candidates in human clinical trials, and we currently face exposure to claims in jurisdictions where we market and distribute Sativex. We may face exposure to claims by an even greater number of persons if we begin marketing and distributing our products commercially in the United States and elsewhere. Now, and in the future, an individual may bring a liability claim against us alleging that Sativex or one of our product candidates caused an injury. While we continue to take what we believe are appropriate precautions, we may be unable to avoid significant liability if any product liability lawsuit is brought against us. Although we have purchased insurance to cover product liability lawsuits, if we cannot successfully defend ourselves against product liability claims, or if such insurance coverage is inadequate, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for Sativex and our other product candidates, if such product candidates are approved;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs of related litigation;
- substantial monetary awards to patients and others;
- increased cost of liability insurance;
- loss of revenue; and
- the inability to successfully commercialize our products.
Counterfeit versions of our products could harm our business.

Counterfeiting activities and the presence of counterfeit products in a number of markets and over the Internet continue to be a challenge for maintaining a safe drug supply for the pharmaceutical industry. Counterfeit products are frequently unsafe or ineffective, and can be life-threatening. To distributors and users, counterfeit products may be visually indistinguishable from the authentic version. Reports of adverse reactions to counterfeit drugs along with increased levels of counterfeiting could be mistakenly attributed to the authentic product, affect patient confidence in the authentic product and harm the business of companies such as ours. If our products were to be the subject of counterfeits, we could incur substantial reputational and financial harm.

We have recently grown our business and will need to further increase the size and complexity of our organization in the future, and we may experience difficulties in managing our growth and executing our growth strategy.

Our management and personnel, systems and facilities currently in place may not be adequate to support our business plan and future growth. With the initiation of Phase 3 clinical trials for Epidiolex and the decision to promote and market in the United States the product candidates for with we receive marketing approval from FDA, we have increased our number of full-time employees from 194 on September 30, 2013 to 470 as of May 31, 2016, primarily because we are conducting all of our Phase 2 and 3 clinical trials of Epidiolex and our other product candidates ourselves and establishing a commercial organization and our commercial infrastructure. As a result of these activities the complexity of our business operations has substantially increased. We will need to further expand our scientific, sales and marketing, managerial, compliance, operational, financial and other resources to support our planned research, development and commercialization activities.

Our need to effectively manage our operations, growth and various projects requires that we:

- continue to improve our operational, financial, management and regulatory compliance controls and reporting systems and procedures;
- attract and retain sufficient numbers of talented employees;
- manage our commercialization activities effectively and in a cost-effective manner;
- manage our clinical trials effectively;
- manage our internal manufacturing operations effectively and in a cost effective manner;
- manage our development efforts effectively while carrying out our contractual obligations to contractors and other third parties; and
- continue to improve our facilities.

In addition, historically, we have utilized and continue to utilize the services of part-time outside consultants and contractors to perform a number of tasks for us, including tasks related to compliance programs, clinical trial management, regulatory affairs, formulation development and other drug development functions. Our growth strategy may also entail expanding our use of consultants and contractors to implement these and other tasks going forward. Because we rely on consultants and contractors for certain functions of our business, we will need to be able to effectively manage these consultants and contractors to ensure that they successfully carry out their contractual obligations and meet expected deadlines. There can be no assurance that we will be able to manage our existing consultants and contractors or find other competent outside expertise, as needed, on economically reasonable terms, or at all. If we are not able to effectively expand our organization by hiring new employees and expanding our use of consultants and contractors, we may be unable to successfully implement the tasks necessary to effectively execute on our planned research, development and commercialization activities and, accordingly, may not achieve our research, development and commercialization goals.
We depend upon our key personnel and our ability to attract and retain employees.

Our future growth and success depend on our ability to recruit, retain, manage and motivate our employees. The inability to hire or retain experienced management personnel could adversely affect our ability to execute our business plan and harm our operating results. Because of the specialized scientific and managerial nature of our business, we rely heavily on our ability to attract and retain qualified scientific, technical and managerial personnel. The competition for qualified personnel in the pharmaceutical field is intense. Due to this intense competition, we may be unable to continue to attract and retain qualified personnel necessary for the development of our business or to recruit suitable replacement personnel.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, comply with applicable manufacturing standards, comply with other federal and state laws and regulations, report information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, or illegal misappropriation of drug product, which could result in serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

If we are unable to use net operating loss carry-forwards and certain built-in losses to reduce future tax payments, or benefit from favorable tax legislation, our business, results of operations and financial condition may be adversely affected.

As a U.K. resident trading company, we are predominantly subject to U.K. corporate taxation. At September 30, 2015, we had cumulative carry-forward tax losses of £74.0 million, available to offset against future profits. The majority of these tax loss attributes have not been recognized on our balance sheet at September 30, 2015. Additionally, as we carry out extensive research and development activities in the U.K., we benefit from the U.K. research and development tax credit regime for small and medium sized companies, whereby our principal research subsidiary, GW Research Ltd., is able to surrender a portion of available losses that arise from research and development activity for a refundable credit of up to approximately 33.4% of the eligible research and development expenditure. We may also benefit in the future from the U.K.’s “patent box” regime, which would allow certain profits attributable to revenue from patented products to be taxed at a lower rate than other profits that over time will be reduced to 10%. When taken in combination with our available carry-forward tax losses and the enhanced relief available on our research and development expenditure, we expect that this may result in a long-term low rate of corporation tax. If, however, we are unable to generate sufficient future taxable profits, or for any reason to utilize our carry-forward losses, or there are unexpected adverse changes to the U.K. research and development tax credit regime or “patent box” regime, or we are unable to qualify for such advantageous tax legislation, our business, results of operations and financial condition may be adversely affected.

We are subject to the U.K. Bribery Act, the U.S. Foreign Corrupt Practices Act and other anti-corruption laws, as well as export control laws, customs laws, sanctions laws and other laws governing our operations. If we fail to comply with these laws, we could be subject to civil or criminal penalties, other remedial measures, and legal expenses, which could adversely affect our business, results of operations and financial condition.

Our operations are subject to anti-corruption laws, including the U.K. Bribery Act 2010, or Bribery Act, the U.S. Foreign Corrupt Practices Act, or FCPA, and other anti-corruption laws that apply in countries where we do business. The Bribery Act, FCPA and these other laws generally prohibit us and our employees and intermediaries from bribing, being bribed or making other prohibited payments to government officials or
other persons to obtain or retain business or gain some other business advantage. We and our commercial partners operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we participate in collaborations and relationships with third parties whose actions could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United Kingdom and the United States, and authorities in the European Union, including applicable export control regulations, economic sanctions on countries and persons, customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws.

However, there is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. Likewise, any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by the United Kingdom, the United States or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

Our proprietary information, or that of our customers, suppliers and business partners, may be lost or we may suffer security breaches.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, clinical trial data, our proprietary business information and that of our customers, suppliers and business partners, and personally identifiable information of our customers, clinical trial subjects and employees, in our data centers and on our networks. The secure processing, maintenance and transmission of this information is critical to our operations. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or breached due to employee error, malfeasance or other disruptions. Although to our knowledge we have not experienced any such material security breach to date, any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, regulatory penalties, disrupt our operations, damage our reputation, and cause a loss of confidence in our products and our ability to conduct clinical trials, which could adversely affect our business and reputation and lead to delays in gaining regulatory approvals for Epidiolex. Although we maintain business interruption insurance coverage, our insurance might not cover all losses from any future breaches of our systems.

Failure of our information technology systems could significantly disrupt the operation of our business.

Our business increasingly depends on the use of information technologies, which means that certain key areas such as research and development, production and sales are to a large extent dependent on our information systems or those of third party providers. Our ability to execute our business plan and to comply with the regulators requirements with respect to data control and data integrity, depends, in part, on the continued and uninterrupted performance of our information technology systems, or IT systems and the IT systems supplied by third-party service providers. These systems are vulnerable to damage from a variety of sources, including telecommunication or network failures, malicious human acts and natural disasters. Moreover, despite network security and backup measures, some of our servers are potentially vulnerable to physical or electronic break-ins, computer viruses and similar disruptive problems. Despite the precautionary measures we and our third-party service providers have taken to prevent unanticipated problems that could affect our IT systems, sustained or repeated system failures or problems arising during the upgrade of any of our IT systems that interrupt our ability to generate and maintain data, and in particular to operate our proprietary technology platform, could adversely affect our ability to operate our business.
Legislative or regulatory reform of the health care system in the United States and foreign jurisdictions may affect our ability to profitably sell our products, if approved.

Our ability to commercialize our future products successfully, alone or with collaborators, will depend in part on the extent to which coverage and reimbursement for the products will be available from government and health administration authorities, private health insurers and other third-party payers. The continuing efforts of the U.S. and foreign governments, insurance companies, managed care organizations and other payers of health care services to contain or reduce health care costs may adversely affect our ability to set prices for our products which we believe are fair, and our ability to generate revenues and achieve and maintain profitability.

Specifically, in both the United States and some foreign jurisdictions, there have been a number of legislative and regulatory proposals to change the health care system in ways that could affect our ability to sell our products profitably. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, enacted in the United States in March 2010, substantially changes the way healthcare is financed by both governmental and private insurers.

We expect additional federal and state proposals and health care reforms to continue to be proposed by legislators, which could limit the prices that can be charged for the products we develop and may limit our commercial opportunity.

The continuing efforts of government and other third-party payers to contain or reduce the costs of health care through various means may limit our commercial opportunity. It will be time consuming and expensive for us to go through the process of seeking coverage and reimbursement from Medicare and private payers. Our products may not be considered cost effective, and government and third-party private health insurance coverage and reimbursement may not be available to patients for any of our future products or sufficient to allow us to sell our products on a competitive and profitable basis. Our results of operations could be adversely affected by ACA and by other health care reforms that may be enacted or adopted in the future. In addition, increasing emphasis on managed care in the United States will continue to put pressure on the pricing of pharmaceutical products. Cost control initiatives could decrease the price that we or any potential collaborators could receive for any of our future products and could adversely affect our ability to generate revenue in the U.S. market and maintain profitability.

In some foreign countries, including major markets in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take six to 12 months or longer after the receipt of regulatory approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a pharmacoeconomic study that compares the cost-effectiveness of our product candidates to other available therapies. Such pharmacoeconomic studies can be costly and the results uncertain. Our business could be harmed if reimbursement of our products is unavailable or limited in scope or amount or if pricing is set at unsatisfactory levels.

We may acquire other companies which could divert our management’s attention, result in additional dilution to our shareholders and otherwise disrupt our operations and harm our operating results.

We may in the future seek to acquire businesses, products or technologies that we believe could complement or expand our product offerings, enhance our technical capabilities or otherwise offer growth opportunities. The pursuit of potential acquisitions may divert the attention of management and cause us to incur various expenses in identifying, investigating and pursuing suitable acquisitions, whether or not they are consummated. If we acquire additional businesses, we may not be able to integrate the acquired personnel, operations and technologies successfully, or effectively manage the combined business following the acquisition. We also may not achieve the anticipated benefits from the acquired business due to a number of factors, including:

• incurrence of acquisition-related costs;
• diversion of management’s attention from other business concerns;
• unanticipated costs or liabilities associated with the acquisition;
In the future, if our acquisitions do not yield expected returns, we may be required to take charges to our operating results arising from the impairment assessment process. Acquisitions may also result in dilutive issuances of equity securities or the incurrence of debt, which could adversely affect our operating results. In addition, if an acquired business fails to meet our expectations, our business, results of operations and financial condition may be adversely affected.

The United Kingdom’s vote in favor of withdrawing from the European Union could lead to increased market volatility which could adversely impact the market price of our ordinary shares and ADSs and make it more difficult for us to do business in Europe.

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union (commonly referred to as “Brexit”). The withdrawal of the United Kingdom from the European Union will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to the EU Treaty. No announcement has been made by the U.K. government as to when it intends to deliver any notice of withdrawal. It appears likely that this withdrawal will involve a process of lengthy negotiations between the United Kingdom and European Union member states to determine the future terms of the United Kingdom’s relationship with the European Union. This could lead to a period of considerable uncertainty particularly in relation to United Kingdom financial and banking markets as well as on the regulatory process in Europe. As a result of this uncertainty, financial markets could experience significant volatility which could adversely affect the market price of our ordinary shares and ADSs.

We may also face new regulatory costs and challenges that could have a material adverse effect on our operations. Depending on the terms of Brexit, the United Kingdom could lose the benefits of global trade agreements negotiated by the European Union on behalf of its members, which may result in increased trade barriers which could make our doing business in Europe more difficult. In addition, currency exchange rates in the pound sterling and the euro with respect to each other and the U.S. dollar have already been adversely affected by Brexit. Should this foreign exchange volatility continue it could cause volatility in our quarterly financial results.

Risks Related to Development and Regulatory Approval of Sativex and Our Product Candidates

Clinical trials for our product candidates are expensive, time-consuming, uncertain and susceptible to change, delay or termination.

Clinical trials are expensive, time consuming and difficult to design and implement. Even if the results of our clinical trials are favorable, the clinical trials for a number of our product candidates are expected to continue for several years and may take significantly longer to complete. In addition, we, the FDA or other regulatory authorities, including state and local authorities, or an Institutional Review Board, or IRB, with respect to a trial at its institution, may suspend, delay or terminate our clinical trials at any time, require us to conduct additional clinical trials, require a particular clinical trial to continue for a longer duration than originally planned, require a change to our development plans such that we conduct clinical trials for a product candidate in a different order, e.g., in a step-wise fashion rather than running two trials of the same product candidate in parallel, or the DEA could suspend or terminate the registrations and quota allotments we require in order to procure and handle controlled substances, for various reasons, including:

- lack of effectiveness of any product candidate during clinical trials;
- discovery of serious or unexpected toxicities or side effects experienced by trial participants or other safety issues, such as drug: drug interactions, including those which cause confounding changes to the levels of other concomitant medications. In this regard it should be noted that the data from the
expanded access studies with Epidiolex we are currently supporting, as presented by Devinsky et al. at the Annual Meeting of the American Epilepsy Society held in December 2015, indicates that Clobazam co-therapy is associated with a higher rate of treatment response (median reduction in convulsive seizures (CBD with v. without Clobazam) at week 12 of treatment. However, this effect is not seen in patients with Dravet syndrome or LGS. We have initiated a Company-sponsored double-blinded, placebo controlled Phase 2 trial to investigate this drug:drug interaction in a controlled and scientific manner;

• slower than expected rates of subject recruitment and enrollment rates in clinical trials;
• difficulty in retaining subjects who have initiated a clinical trial but may withdraw at any time due to adverse side effects from the therapy, insufficient efficacy, fatigue with the clinical trial process or for any other reason;
• delays or inability in manufacturing or obtaining sufficient quantities of materials for use in clinical trials due to regulatory and manufacturing constraints;
• inadequacy of or changes in our manufacturing process or product formulation;
• delays in obtaining regulatory authorization to commence a trial, including “clinical holds” or delays requiring suspension or termination of a trial by a regulatory agency, such as the FDA, before or after a trial is commenced;
• DEA-related recordkeeping, reporting or security violations at a clinical site, leading the DEA or state authorities to suspend or revoke the site’s controlled substance license and causing a delay or termination of planned or ongoing trials;
• changes in applicable regulatory policies and regulation, including changes to requirements imposed on the extent, nature or timing of studies;
• delays or failure in reaching agreement on acceptable terms in clinical trial contracts or protocols with prospective clinical trial sites;
• uncertainty regarding proper dosing;
• delay or failure to supply product for use in clinical trials which conforms to regulatory specification;
• unfavorable results from ongoing pre-clinical studies and clinical trials;
• failure of our contract research organizations, or CROs, or other third-party contractors to comply with all contractual requirements or to perform their services in a timely or acceptable manner;
• failure by us, our employees, our CROs or their employees to comply with all applicable FDA or other regulatory requirements relating to the conduct of clinical trials or the handling, storage, security and recordkeeping for controlled substances;
• scheduling conflicts with participating clinicians and clinical institutions;
• failure to design appropriate clinical trial protocols;
• regulatory concerns with cannabinoid products generally and the potential for abuse;
• insufficient data to support regulatory approval;
• inability or unwillingness of medical investigators to follow our clinical protocols; or
• difficulty in maintaining contact with patients during or after treatment, which may result in incomplete data.

Any of the foregoing could have a material adverse effect on our business, results of operations and financial condition.
Any failure by us to comply with existing regulations could harm our reputation and operating results.

We are subject to extensive regulation by U.S. federal and state and foreign governments in each of the markets where we currently sell Sativex or in markets where we have product candidates progressing through the approval process. We must adhere to all regulatory requirements including the FDA’s Good Laboratory Practice, current Good Manufacturing Practice, or cGMP, and Good Clinical Practice requirements. If we or our suppliers fail to comply with applicable regulations, including FDA pre-or post-approval cGMP requirements, then the FDA or other foreign regulatory authorities could sanction us. Even if a drug is FDA-approved, regulatory authorities may impose significant restrictions on a product’s indicated uses or marketing or impose ongoing requirements for potentially costly post-marketing trials.

If any of our product candidates is approved in the United States, it will be subject to ongoing regulatory requirements for labeling, packaging, storage, distribution, import, export, advertising, promotion, sampling, recordkeeping and submission of safety and other post-market information, including both federal and state requirements in the United States. In addition, manufacturers and manufacturers’ facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMP. As such, we and our contract manufacturers (in the event contract manufacturers are appointed in the future) are subject to continual review and periodic inspections to assess compliance with cGMP. Accordingly, we and others with whom we work must continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, quality control and quality assurance. We will also be required to report certain adverse reactions and production problems, if any, to the FDA, and to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product’s approved label.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of the product, it may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If we fail to comply with applicable regulatory requirements, a regulatory agency or enforcement authority may:

- issue warning letters;
- impose civil or criminal penalties;
- suspend regulatory approval;
- suspend any of our ongoing clinical trials;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including by requiring us to enter into a Corporate Integrity Agreement or closing our contract manufacturers’ facilities, if any; or
- seize or detain products or require a product recall.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenue from Sativex and our product candidates. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our business and our operating results will be adversely affected. Additionally, if we are unable to generate revenue from sales of Sativex, our potential for achieving profitability will be diminished and the capital necessary to fund our operations will be increased.

Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses, divert our management’s attention from the operation of our business and damage our reputation. We expend significant resources on compliance efforts and such expenses are unpredictable and might adversely affect our results. Changing laws, regulations and standards might also create uncertainty, higher expenses and increase insurance costs. As a result, we intend to invest all reasonably necessary resources to comply with evolving standards, and this investment might result in increased...
management and administrative expenses and a diversion of management time and attention from revenue-generating activities to compliance activities.

Information obtained from expanded access studies may not reliably predict the efficacy of our product candidates in company-sponsored clinical trials and may lead to adverse events that could limit approval.

The expanded access studies we are currently supporting are uncontrolled, carried out by individual investigators and not typically conducted in strict compliance with GCPs, all of which can lead to a treatment effect which may differ from that in placebo-controlled trials. These studies provide only anecdotal evidence of efficacy for regulatory review. These studies contain no control or comparator group for reference and these patient data are not designed to be aggregated or reported as study results. Moreover, data from such small numbers of patients may be highly variable. Information obtained from these studies, including the statistical principles that we and the independent investigators have chosen to apply to the data, may not reliably predict data collected via systematic evaluation of the efficacy in company-sponsored clinical trials or evaluated via other statistical principles that may be applied in those trials. Reliance on such information to design our clinical trials may lead to Phase 2 and 3 trials that are not adequately designed to demonstrate efficacy and could delay or prevent our ability to seek approval of Epidiolex.

Expanded access programs provide supportive safety information for regulatory review. Physicians conducting these studies may use Epidiolex in a manner inconsistent with the protocol, including in children with conditions beyond those being studied in GW-sponsored trials. Any adverse events or reactions experienced by subjects in the expanded access program may be attributed to Epidiolex and may limit our ability to obtain regulatory approval with labeling that we consider desirable, or at all.

There is a high rate of failure for drug candidates proceeding through clinical trials.

Generally, there is a high rate of failure for drug candidates proceeding through clinical trials. We may suffer significant setbacks in our clinical trials similar to the experience of a number of other companies in the pharmaceutical and biotechnology industries, even after receiving promising results in earlier trials. In this regard, the results of none of the three Phase 3 cancer pain trials for Sativex showed a statistically significant difference for Sativex compared with placebo even though the results of the preceding Phase 2 cancer pain trials for Sativex did show positive results. Further, even if we view the results of a clinical trial to be positive, the FDA or other regulatory authorities may disagree with our interpretation of the data. In the event that we obtain negative results from clinical trials for Epidiolex or our other product candidates, or the FDA places a clinical hold on our trials due to potential Chemistry, Manufacturing and Controls issues or other hurdles or does not approve our NDA for our product candidates, we may not be able to generate sufficient revenue or obtain financing to continue our operations, our ability to execute on our current business plan will be materially impaired, our reputation in the industry and in the investment community would likely be significantly damaged and the price of our ADSs would likely decrease significantly. In addition, our inability to properly design, commence and complete clinical trials may negatively impact the timing and results of our clinical trials and ability to seek approvals for our drug candidates.

The anticipated development of a Risk Evaluation and Mitigation Strategy (REMS) for our product candidates could cause delays in the approval process and would add additional layers of regulatory requirements that could impact our ability to commercialize our product candidates in the United States and reduce their market potential.

As a condition of approval of an NDA, the FDA may require a Risk Evaluation and Mitigation Strategies (REMS) to ensure that the benefits of the drug outweigh the potential risks. REMS elements can include medication guides, communication plans for health care professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patient registries. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug’s safety or efficacy. We may be required to adopt a REMS for our product candidates to ensure that the benefits outweigh the risks of abuse, misuse, diversion and other potential safety concerns. Even if abuse, misuse and diversion are not as high as for other cannabinoid products, there can be no assurance that the FDA will approve a manageable REMS for our product candidates, which could create material and
significant limits on our ability to successfully commercialize our product candidates in the United States. Delays in the REMS approval process could result in delays in the NDA approval process. In addition, as part of the REMS, the FDA could require significant restrictions, such as restrictions on the prescription, distribution and patient use of the product, which could significantly impact our ability to effectively commercialize our product candidates, and dramatically reduce their market potential thereby adversely impacting our business, financial condition and results of operations. Even if initial REMS are not highly restrictive, if, after launch, our product candidates were to be subject to significant abuse/non-medical use or diversion from licit channels, this could lead to negative regulatory consequences, including a more restrictive REMS.

If we are found in violation of federal or state “fraud and abuse” laws, we may be required to pay a penalty and/or be suspended from participation in federal or state health care programs, which may adversely affect our business, financial condition and results of operations.

After we obtain regulatory approval for our products in the United States, if any, we will be subject to various federal and state health care “fraud and abuse” laws, including anti-kickback laws, false claims laws and other laws intended to reduce fraud and abuse in federal and state health care programs, which could affect us particularly upon successful commercialization of our products in the United States. The Medicare and Medicaid Patient Protection Act of 1987, or federal Anti-Kickback Statute, makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf), to knowingly and willfully solicit, receive, offer or pay any remuneration that is intended to induce the referral of business, including the purchase, order or prescription of a particular drug for which payment may be made under a federal health care program, such as Medicare or Medicaid. Under federal government regulations, some arrangements, known as safe harbors, are deemed not to violate the federal Anti-Kickback Statute. Although we seek to structure our business arrangements in compliance with all applicable requirements, these laws are broadly written, and it is often difficult to determine precisely how the law will be applied in specific circumstances. Accordingly, it is possible that our practices may be challenged under the federal Anti-Kickback Statute. False claims laws prohibit anyone from knowingly and willfully presenting or causing to be presented for payment to third-party payers, including government payers, claims for reimbursed drugs or services that are false or fraudulent, claims for items or services that were not provided as claimed, or claims for medically unnecessary items or services. Cases have been brought under false claims laws alleging that off-label promotion of pharmaceutical products or the provision of kickbacks has resulted in the submission of false claims to governmental health care programs. Under the Health Insurance Portability and Accountability Act of 1996, we are prohibited from knowingly and willfully executing a scheme to defraud any health care benefit program, including private payers, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for health care benefits, items or services. Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including fines and/or exclusion or suspension from federal and state health care programs such as Medicare and Medicaid and debarment from contracting with the U.S. government. In addition, private individuals have the ability to bring actions on behalf of the government under the federal False Claims Act as well as under the false claims laws of several states.

Many states have adopted laws similar to the federal anti-kickback statute, some of which apply to the referral of patients for health care services reimbursed by any source, not just governmental payers. In addition, California and a few other states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America Code on Interactions with Healthcare Professionals. In addition, several states impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. There are ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement we could be subject to penalties.

Neither the government nor the courts have provided definitive guidance on the application of fraud and abuse laws to our business. Law enforcement authorities are increasingly focused on enforcing these laws, and it is possible that some of our practices may be challenged under these laws. While we believe we have structured our business arrangements to comply with these laws, it is possible that the government could
Our ability to research, develop and commercialize Sativex and our product candidates is dependent on our ability to maintain licenses relating to the cultivation, possession and supply of controlled substances.

Our research and manufacturing facilities are located exclusively in the United Kingdom. In the United Kingdom, licenses to cultivate, possess and supply cannabis for medical research are granted by the Home Office on an annual basis. Although the Home Office has renewed our licenses each year since 1998, it may not do so in the future, in which case we may not be in a position to carry on our research and development program in the United Kingdom. In addition, we are required to maintain our existing commercial licenses to cultivate, produce and supply cannabis. However, if the Home Office were not prepared to renew such licenses, we would be unable to manufacture and distribute our products on a commercial basis in the United Kingdom or beyond. In order to carry out research in countries other than the United Kingdom, similar licenses to those outlined above are required to be issued by the relevant authority in each country. In addition, we will be required to obtain licenses to export from the United Kingdom and to import into the recipient country. To date, we have obtained necessary import and export licenses to 37 countries. Although we have an established track record of successfully obtaining such licenses as required, this may change in the future.

In the United States, the DEA regulates the cultivation, possession and supply of cannabis for medical research and/or commercial development, including the requirement of annual registrations to manufacture or distribute pharmaceutical products derived from cannabis extracts. We do not currently conduct manufacturing or repackaging/relabeling of any product candidates in the United States. In the event that we sought to do so in the future, a decision to manufacture, or supply cannabis extracts for medical research or commercial development in the United States would require that we and/or our contract manufacturers maintain such registrations, and be subject to other regulatory requirements such as manufacturing quotas, and if the DEA failed to issue or renew such registrations, we would be unable to manufacture and distribute any product in the United States on a commercial basis.

Serious adverse events or other safety risks could require us to abandon development and preclude, delay or limit approval of our product candidates, or limit the scope of any approved label or market acceptance.

If Sativex or any of our product candidates, prior to or after any approval for commercial sale, cause serious or unexpected side effects, or are associated with other safety risks such as misuse, abuse or diversion, a number of potentially significant negative consequences could result, including:

- regulatory authorities may interrupt, delay or halt clinical trials;
- regulatory authorities may deny regulatory approval of our product candidates;
- regulatory authorities may require certain labeling statements, such as warnings or contraindications or limitations on the indications for use, and/or impose restrictions on distribution in the form of a Risk Evaluation and Mitigation Strategy, or REMS, in connection with approval, if any;
- regulatory authorities may withdraw their approval, require more onerous labeling statements or impose a more restrictive REMS of any product that is approved;
- we may be required to change the way the product is administered or conduct additional clinical trials;
- our relationships with our collaboration partners may suffer;
- we could be sued and held liable for harm caused to patients; or
- our reputation may suffer. The reputational risk is heightened with respect to those of our product candidates that are being developed for pediatric indications,
We may voluntarily suspend or terminate our clinical trials if at any time we believe that they present an unacceptable risk to participants or if preliminary data demonstrate that our product candidates are unlikely to receive regulatory approval or unlikely to be successfully commercialized. To date, we have only voluntarily suspended clinical trials when recruitment of the target patients has proven to be too difficult or, temporarily, to properly investigate suspected adverse events. In addition, regulatory agencies, IRBs or data safety monitoring boards may at any time recommend the temporary or permanent discontinuation of our clinical trials or request that we cease using investigators in the clinical trials if they believe that the clinical trials are not being conducted in accordance with applicable regulatory requirements, or that they present an unacceptable safety risk to participants. Although we have never been asked by a regulatory agency, IRB or data safety monitoring board to temporarily or permanently discontinue a clinical trial, if we elect or are forced to suspend or terminate a clinical trial of any of our product candidates, the commercial prospects for that product will be harmed and our ability to generate product revenue from that product may be delayed or eliminated. Furthermore, any of these events may result in labeling statements such as warnings or contraindications. In addition, such events or labeling could prevent us or our partners from achieving or maintaining market acceptance of the affected product and could substantially increase the costs of commercializing our product candidates and impair our ability to generate revenue from the commercialization of these products either by us or by our collaboration partners.

If third parties claim that intellectual property used by us infringes upon their intellectual property, our operating profits could be adversely affected.

There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the pharmaceutical industry. We may, from time to time, be notified of claims that we are infringing upon patents, trademarks, copyrights or other intellectual property rights owned by third parties, and we cannot provide assurances that other companies will not, in the future, pursue such infringement claims against us or any third-party proprietary technologies we have licensed. If we were found to infringe upon a patent or other intellectual property right, or if we failed to obtain or renew a license under a patent or other intellectual property right from a third party, or if a third party that we were licensing technologies from was found to infringe upon a patent or other intellectual property rights of another third party, we may be required to pay damages, including triple damages if the infringement is found to be willful, suspend the manufacture of certain products or reengineer or rebrand our products, if feasible, or we may be unable to enter certain new product markets. Any such claims could also be expensive and time consuming to defend and divert management’s attention and resources. Our competitive position could suffer as a result. In addition, if we have declined to enter into a valid non-disclosure or assignment agreement for any reason, we may not own the invention or our intellectual property, and our products may not be adequately protected. Although we have reviewed certain third-party patents and patent filings that we believe may be relevant to Sativex, Epidiolex and our other product candidates, we have not conducted full freedom-to-operate searches or analyses, and we may not be aware of patents or pending or future patent applications that, if issued, would block us from commercializing Sativex, Epidiolex or our other product candidates. Thus, we cannot guarantee that Sativex, Epidiolex or our other product candidates, or our commercialization thereof, does not and will not infringe any third party’s intellectual property.

Risks Related to Our Reliance Upon Third Parties

We depend substantially on the commercial expertise of our collaboration partners for Sativex.

Although we intend to commercialize Epidiolex using our own sales and marketing operation in the United States and potentially elsewhere, we rely on the expertise and commercial skills of our collaboration partners to sell Sativex. We have entered into agreements for the commercialization of Sativex with Almirall S.A., or Almirall, in Europe (excluding the United Kingdom) and Mexico; Otsuka, in the United States; Novartis Pharma AG, or Novartis, in Australia and New Zealand, Asia (excluding Japan, China and Hong Kong), the Middle East (excluding Israel) and Africa; Bayer HealthCare AG in the United Kingdom and Canada; Ipsen Biopharm Ltd, or Ipsen, in Latin America (excluding Mexico and the Islands of the Caribbean); and Neopharm Group in Israel. Our ability to successfully market and sell Sativex in each of these markets depends entirely on the expertise and commercial skills of our collaboration partners. Our partners have the right, under certain circumstances, to terminate their agreements with us, and three of our partners, Almirall,
Otsuka and Novartis, have the right to terminate their agreements with us without cause. No partner has given notice of termination of their agreement with us to date, but given the fact that not one of three Phase 3 cancer pain trials for Sativex showed a statistically significant difference for Sativex compared with placebo, we cannot be certain that not one of these partners will not terminate their agreement with us. Further, a failure by our partners to successfully market Sativex, or the termination of agreements with our partners, may have an adverse effect on our business at least in the near term period following such termination.

We have relied on Otsuka for funding of our Sativex research and development programs in the United States and if Otsuka were to terminate its agreement with us we would have to fund any future development of Sativex in the United States ourselves, and come to an agreement with Otsuka on jointly-owned intellectual property resulting from our pre-clinical research collaboration.

Under the terms of our agreement with Otsuka with respect to Sativex in the United States, Otsuka funds all pre-clinical and clinical trials for the development of Sativex in the treatment of cancer pain as well as potential additional indications. There is however no assurance that Otsuka will agree to fund future development activities. As outlined above, Otsuka has the right to terminate their agreement with us without cause. In light of the results of the Phase 3 cancer pain trials for Sativex discussed above, we cannot be certain that Otsuka will not terminate this agreement. If Otsuka were to terminate this agreement, we would be required to find alternative funding for our clinical program for any future development of Sativex in the United States.

In addition, under the terms of the research collaboration agreement we entered with Otsuka in 2007 all intellectual property rights (including both patents and non-manufacturing related know-how) that was conceived by either Otsuka or us during the course of the collaboration is to be jointly owned by Otsuka and us unless Otsuka elects to cease funding the prosecution and maintenance costs for these rights. As at May 31, 2016 we had 6 patent families which consist of 81 jointly owned patent applications and 73 granted patents relating to our collaboration with Otsuka. Because Otsuka exercises some control over this jointly owned intellectual property, we may need to seek Otsuka’s consent to out-license and/or enforce some of this collaboration intellectual property in the future.

Our existing collaboration arrangements and any that we may enter into in the future may not be successful, which could adversely affect our ability to develop and commercialize Sativex and our product candidates.

We are a party to, and may seek additional, collaboration arrangements with pharmaceutical or biotechnology companies for the development or commercialization of Sativex and our product candidates. We may, with respect to our product candidates, enter into new arrangements on a selective basis depending on the merits of retaining commercialization rights for ourselves as compared to entering into selective collaboration arrangements with leading pharmaceutical or biotechnology companies for each product candidate, both in the United States and internationally. To the extent that we decide to enter into collaboration agreements, we will face significant competition in seeking appropriate collaborators. Moreover, collaboration arrangements are complex and time consuming to negotiate, document and implement. We may not be successful in our efforts to establish, implement and maintain collaborations or other alternative arrangements if we choose to enter into such arrangements and, as noted above, our selected partners may be given, and may exercise, a right to terminate their agreement with us without cause. The terms of any collaboration or other arrangements that we may establish may not be favorable to us.

Any existing or future collaboration that we enter into may not be successful. The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations. For example, we have amended our agreement with Novartis, our collaborator for Sativex in parts of Asia, the Middle East and Africa, in order to permit Novartis not to make a determination about launching Sativex in any country in its territory until final data is available for the Phase 3 clinical trials for Sativex in cancer pain. In light of the results of these trials, there is a likelihood that Novartis will terminate their agreement with us.
Disagreements between parties to a collaboration arrangement regarding development, intellectual property, regulatory or commercialization matters, can lead to delays in the development process or commercialization of the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision making authority.

Collaborations with pharmaceutical or biotechnology companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation.

*We depend on a limited number of suppliers for materials and components required to manufacture Sativex and our other product candidates. The loss of these suppliers, or their failure to supply us on a timely basis, could cause delays in our current and future capacity and adversely affect our business.*

We depend on a limited number of suppliers for the materials and components required to manufacture Sativex and our other product candidates. For example, we rely on single-source suppliers to supply various components of Sativex, including the glass vial and pump actuator, and we rely on a single contractor for commercial supply of botanical raw material for Sativex. Although we are actively working on expanding the number of suppliers and facilities for Epidiolex production, at present we have two independent contractors who supply botanical raw material for Epidiolex but are otherwise dependent on single-source suppliers and facilities for producing Epidiolex. As a result, we may not be able to obtain sufficient quantities of critical materials and components in the future. A delay or interruption by our suppliers may also harm our business, results of operations and financial condition. In addition, the lead time needed to establish a relationship with a new supplier can be lengthy, and we may experience delays in meeting demand in the event we must switch to a new supplier. The time and effort to qualify for and, in some cases, obtain regulatory approval for a new supplier could result in additional costs, diversion of resources or reduced manufacturing yields, any of which would negatively impact our operating results. Our dependence on single-source suppliers exposes us to numerous risks, including the following: our suppliers may cease or reduce production or deliveries, raise prices or renegotiate terms; our suppliers may become insolvent or cease trading; we may be unable to locate a suitable replacement supplier on acceptable terms or on a timely basis, or at all; and delays caused by supply issues may harm our reputation, frustrate our customers and cause them to turn to our competitors for future needs.

*A significant portion of our cash and cash equivalents are held at a small number of banks.*

A significant portion of our cash and cash equivalents is presently held at a small number of banks. Although our board has adopted a treasury policy requiring us to limit the amount of cash held by each banking group taking into account their credit ratings, we are subject to credit risk if any of these banks are unable to repay the balance in the applicable account or deliver our securities or if any bank should become bankrupt or otherwise insolvent. Any of the above events could have a material and adverse effect on our business, results of operations and financial condition.

**Risks Related to Our Intellectual Property**

*We may not be able to adequately protect Sativex, our product candidates or our proprietary technology in the marketplace.*

Our success will depend, in part, on our ability to obtain patents, protect our trade secrets and operate without infringing on the proprietary rights of others. We rely upon a combination of patents, trade secret protection (i.e., know how), and confidentiality agreements to protect the intellectual property of Sativex and our product candidates. The strengths of patents in the pharmaceutical field involve complex legal and scientific questions and can be uncertain. Where appropriate, we seek patent protection for certain aspects of our products and technology. Filing, prosecuting and defending patents throughout the world would be prohibitively expensive, so our policy is to patent commercially potential technology in jurisdictions with significant commercial opportunities. However, patent protection may not be available for some of the products or technology we are developing. If we must spend significant time and money protecting, defending or enforcing our patents, designing around patents held by others or licensing, potentially for large fees, patents or other proprietary rights held by others, our business, results of operations and financial condition may be harmed. We may not develop additional proprietary products that are patentable.
The patent positions of pharmaceutical products are complex and uncertain. The scope and extent of patent protection for Sativex and our product candidates are particularly uncertain. To date, our principal product candidates, including Sativex and Epidiolex, have been based on specific formulations of certain previously known cannabinoids found in nature in the cannabis sativa plant. While we have sought patent protection directed to, among other things, composition of matter for our specific formulations, their methods of use, and methods of manufacture, we do not have and will not be able to obtain composition of matter protection on these previously known cannabinoids per se. We anticipate that the products we develop in the future will continue to include or be based on the same or other naturally occurring compounds, as well as synthetic compounds we may discover. Although we have sought and expect to continue to seek patent protection for our product candidates, their methods of use, and methods of manufacture, any or all of them may not be subject to effective patent protection. Publication of information related to Sativex and our product candidates by us or others may prevent us from obtaining or enforcing patents relating to these products and product candidates. Furthermore, others may independently develop similar products, may duplicate our products, or may design around our patent rights. In addition, any of our issued patents may be opposed and/or declared invalid or unenforceable. Indeed, two of our recently issued European patents, including our European patent claiming the use of CBD in the treatment of partial seizures, have received notices of opposition which may result in claims in either or both of these patents being narrowed or cancelled such that the scope of an opposed patent may not be as broad, or the opposed patent may be revoked in its entirety. If we fail to adequately protect our intellectual property, we may face competition from companies who attempt to create a generic product to compete with Sativex or Epidiolex. We may also face competition from companies who develop a substantially similar product to Sativex, Epidiolex or one of our other product candidates that is not covered by any of our patents.

Many companies have encountered significant problems in protecting, defending and enforcing intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property rights, particularly those relating to pharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

Risks Related to Controlled Substances

Controlled substance legislation differs between countries and legislation in certain countries may restrict or limit our ability to sell Sativex and our product candidates.

Most countries are parties to the Single Convention on Narcotic Drugs 1961, which governs international trade and domestic control of narcotic substances, including cannabis extracts. Countries may interpret and implement their treaty obligations in a way that creates a legal obstacle to our obtaining regulatory approval for Sativex, Epidiolex and our other products in those countries. These countries may not be willing or able to amend or otherwise modify their laws and regulations to permit Sativex, Epidiolex or our other products to be marketed, or achieving such amendments to the laws and regulations may take a prolonged period of time. For example, we are currently unable to file a regulatory application in Mexico or Japan due to a national law which the regulators consider prevents the approval of a cannabis-based medicine. In the case of countries with similar obstacles, we would be unable to market Sativex, Epidiolex and our product candidates in countries in the near future or perhaps at all if the laws and regulations in those countries do not change.

The product candidates we are developing will be subject to U.S. controlled substance laws and regulations and failure to comply with these laws and regulations, or the cost of compliance with these laws and regulations, may adversely affect the results of our business operations, both during clinical development and post approval, and our financial condition.

The product candidates we are developing contain controlled substances as defined in the federal Controlled Substances Act of 1970, or CSA. Controlled substances that are pharmaceutical products are subject to a high degree of regulation under the CSA, which establishes, among other things, certain registration, manufacturing quotas, security, recordkeeping, reporting, import, export and other requirements administered by the DEA. The DEA classifies controlled substances into five schedules: Schedule I, II, III, IV.
or V substances. Schedule I substances by definition have a high potential for abuse, no currently “accepted medical use” in the United States, lack accepted safety for use under medical supervision, and may not be prescribed, marketed or sold in the United States. Pharmaceutical products approved for use in the United States which contain a controlled substance are listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest potential for abuse or dependence and Schedule V substances the lowest relative risk of abuse among such substances. Schedule I and II drugs are subject to the strictest controls under the CSA, including manufacturing and procurement quotas, security requirements and criteria for importation. In addition, dispensing of Schedule II drugs is further restricted. For example, they may not be refilled without a new prescription.

While cannabis is a Schedule I controlled substance, products approved for medical use in the United States that contain cannabis or cannabis extracts should be placed in Schedules II-V, since approval by the FDA satisfies the “accepted medical use” requirement. If and when any of our product candidates receive FDA approval, the DEA will make a scheduling determination and place the product in a schedule other than Schedule I in order for it to be prescribed to patients in the United States. If approved by the FDA, we expect the finished dosage form of Epidiolex to be controlled in Schedule III or IV. Consequently, the manufacture, importation, exportation, domestic distribution, storage, sale and legitimate use will be subject to specific and potentially significant levels of regulation by the DEA. On November 25, 2015 the President of the United States signed a new law that (i) amends the CSA to require the DEA to issue an interim final scheduling rule within ninety days following FDA approval and the Secretary of Health and Human Services recommending that the Attorney General control the drug in Schedule II, III, IV or V, and (ii) amends the FDCA to ensure that companies do not lose exclusivity on newly approved drugs because of the DEA drug scheduling process. Insys Therapeutics Inc., a competitor who is developing products for the treatment of Dravet Syndrome and LGS (among other indications) which are based on CBD produced by a synthetic process, has already petitioned DEA to reschedule its synthetic CBD. Any DEA rescheduling action on the Insys petition might be limited to CBD produced by a synthetic process and thereby not apply to our product. If Insys succeeds with its petition before our product is approved by FDA, it will avoid the 90-day post-FDA approval rescheduling delay. Furthermore, if the FDA, DEA, or any foreign regulatory authority determines that Sativex or Epidiolex may have potential for abuse, it may require us to generate more clinical or other data than we currently anticipate to establish whether or to what extent the substance has an abuse potential, which could increase the cost and/or delay the launch of that product.

**DEA registration and inspection of facilities.** Facilities conducting research, manufacturing, distributing, importing or exporting, or dispensing controlled substances must be registered (licensed) to perform these activities and have the security, control, recordkeeping, reporting and inventory mechanisms required by the DEA to prevent drug loss and diversion. All these facilities must renew their registrations annually, except dispensing facilities, which must renew every three years. The DEA conducts periodic inspections of certain registered establishments that handle controlled substances. Obtaining the necessary registrations may result in delay of the importation, manufacturing or distribution of Sativex and/or Epidiolex. Furthermore, failure to maintain compliance with the CSA, particularly non-compliance resulting in loss or diversion, can result in regulatory action that could have a material adverse effect on our business, financial condition and results of operations. The DEA may seek civil penalties, refuse to renew necessary registrations, or initiate proceedings to restrict, suspend or revoke those registrations. In certain circumstances, violations could lead to criminal proceedings.

**State-controlled substances laws.** Individual states have also established controlled substance laws and regulations. Though state-controlled substances laws often mirror federal law, because the states are separate jurisdictions, they may separately schedule our product candidates as well. While some states automatically schedule a drug based on federal action, other states schedule drugs through rulemaking or a legislative action. State scheduling may delay commercial sale of any product for which we obtain federal regulatory approval and adverse scheduling could have a material adverse effect on the commercial attractiveness of such product. We or our partners must also obtain separate state registrations, permits or licenses in order to be able to obtain, handle, and distribute controlled substances for clinical trials or commercial sale, and failure to meet applicable regulatory requirements could lead to enforcement and sanctions by the states in addition to those from the DEA or otherwise arising under federal law.
Clinical trials. Because Sativex and Epidiolex contain cannabis extracts, which are Schedule I substances, to conduct clinical trials with Sativex and Epidiolex in the United States prior to approval, each of our research sites must submit a research protocol to the DEA and obtain a DEA researcher registration that will allow those sites to handle and dispense Sativex and/or Epidiolex (as applicable) and to obtain the product from our importer. If the DEA delays or denies the grant of a research registration to one or more research sites, the clinical trial could be significantly delayed, and we could lose clinical trial sites. The importer for the clinical trials must also obtain a Schedule I importer registration and an import permit for each import. We do not currently conduct any manufacturing or repackaging/relabeling of either Sativex or its active ingredients (i.e., the cannabis extract) or Epidiolex or its active ingredient (purified CBD) in the United States. Sativex and Epidiolex are both imported in fully-finished, packaged and labeled dosage forms.

Importation. If one of our product candidates is approved and classified as a Schedule II or III substance, an importer can import for commercial purposes if it obtains an importer registration and files an application for an import permit for each import. The DEA provides annual assessments/estimates to the International Narcotics Control Board which guides the DEA in the amounts of controlled substances that the DEA authorizes to be imported. The failure to identify an importer or obtain the necessary import authority, including specific quantities, could affect product availability and have a material adverse effect on our business, results of operations and financial condition. In addition, an application for a Schedule II importer registration must be published in the Federal Register, and there is a waiting period for third party comments to be submitted. It is always possible a competitor could take this opportunity to make adverse comments that delay the grant of an importer registration.

If one of our product candidates is approved and classified as a Schedule II controlled substance, federal law may prohibit the import of the substance for commercial purposes. If a product is listed as a Schedule II substance, we will not be allowed to import that drug for commercial purposes unless the DEA determines that domestic supplies are inadequate or there is inadequate domestic competition among domestic manufacturers for the substance as defined by the DEA. It is always possible the DEA could find that the active substance in a product, even if it is a plant derived substance, could be manufactured in the US. Moreover, Schedule I controlled substances, including BDSs, have never been registered with the DEA for importation commercial purposes, only for scientific and research needs. Therefore, if neither Sativex nor its BDSs, nor Epidiolex or its purified BDS could be imported, that product would have to be wholly manufactured in the United States, and we would need to secure a manufacturer that would be required to obtain and maintain a separate DEA registration for that activity.

Manufacture in the United States. If, because of a Schedule II classification or voluntarily, we were to conduct manufacturing or repackaging/relabeling in the United States, our contract manufacturers would be subject to the DEA’s annual manufacturing and procurement quota requirements. Additionally, regardless of the scheduling of Sativex and Epidiolex, cannabis and the BDSs comprising the active ingredient in the final dosage form are currently Schedule I controlled substances and would be subject to such quotas as these substances could remain listed on Schedule I. The annual quota allocated to us or our contract manufacturers for the active ingredients in our products may not be sufficient to complete clinical trials or meet commercial demand. Consequently, any delay or refusal by the DEA in establishing our, or our contract manufacturers’, procurement and/or production quota for controlled substances could delay or stop our clinical trials or product launches, which could have a material adverse effect on our business, financial position and operations.

Distribution in the United States. If any of our product candidates is scheduled as Schedule II or III, we would also need to identify wholesale distributors with the appropriate DEA and state registrations and authority to distribute the product to pharmacies and other health care providers. We would need to identify distributors to distribute the product to pharmacies; these distributors would need to obtain Schedule II or III distribution registrations. The failure to obtain, or delay in obtaining, or the loss any of those registrations could result in increased costs to us. If any of our product candidates is a Schedule II drug, pharmacies would have to maintain enhanced security with alarms and monitoring systems and they must adhere to recordkeeping and inventory requirements. This may discourage some pharmacies from carrying either or both of these products. Furthermore, state and federal enforcement actions, regulatory requirements, and legislation...
intended to reduce prescription drug abuse, such as the requirement that physicians consult a state prescription drug monitoring program may make physicians less willing to prescribe, and pharmacies to dispense, Schedule II products.

**The approval and use of medical and recreational marijuana in various U.S. states may impact our business.**

There is a substantial amount of change occurring in various states of the United States regarding the use of medical and recreational marijuana. While marijuana is a Schedule I substance as defined under federal law, and its possession and use is not permitted according to federal law, a number of individual states have enacted state laws to enable possession and use of marijuana for medical purposes, and in some states for recreational purposes also. Our business is quite distinct from that of crude herbal marijuana, however, our prospects may be impacted by developments of these laws at the state level in the United States.
GW Pharmaceuticals Announces Proposed Public Offering of ADSs

London, UK, 12 July 2016: GW Pharmaceuticals plc (Nasdaq: GWPH, AIM: GWP, "GW" or the “Company’’), a biopharmaceutical company focused on discovering, developing and commercializing novel therapeutics from its proprietary cannabinoid product platform, announced today that it intends to sell, subject to market and other conditions, $150,000,000 of American Depositary Shares (“ADSs”) representing ordinary shares of GW on the NASDAQ Global Market in an underwritten U.S. public offering. GW expects to grant the underwriters a 30-day option to purchase up to an additional $22,500,000 of ADSs at the offering price. There can be no assurance as to whether or when the offering may be completed, or as to the actual size or terms of the offering. The price for the offering has not yet been determined.

Morgan Stanley, BofA Merrill Lynch and Goldman, Sachs & Co. are acting as joint book-running managers for the offering. Cowen and Company is acting as lead manager and Piper Jaffray is acting as manager.

The ADSs described above are being offered by GW pursuant to a shelf registration statement filed by GW with the Securities and Exchange Commission (“SEC”) that became automatically effective on May 7, 2014. A preliminary prospectus supplement related to the offering has been filed with the SEC and is available on the SEC’s website at http://www.sec.gov. Copies of the preliminary prospectus supplement and the accompanying prospectus relating to this offering may be obtained from Morgan Stanley & Co. LLC, Attention: Prospectus Department, 180 Varick Street, 2nd Floor, New York, New York 10014; BofA Merrill Lynch, NC1-004-03-43, 200 North College Street, 3rd Floor, Charlotte, NC 28255-0001, Attention: Prospectus Department, email: dg.prospectus_requests@baml.com; or from Goldman, Sachs & Co., Attention: Prospectus Department, 200 West Street, New York, NY 10282, telephone: 1-866-471-2526, facsimile: 212-902-9316 or by emailing prospectus-ny@ny.email.gs.com.
This press release shall not constitute an offer to sell or the solicitation of an offer to buy nor shall there be any sale of these securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

There will be no offer of ADSs to the public in the UK. This press release is not directed to, or intended for distribution or use by, any person or entity that is a citizen or resident or located in any locality, state, country or other jurisdiction where such distribution, publication, availability or use would be contrary to law or regulation or which would require any registration or licensing within such jurisdiction.

The distribution of this press release into jurisdictions other than the UK may be restricted by law. Persons into whose possession this announcement come should inform themselves about and observe any such restrictions.

For readers in the European Economic Area

In any EEA Member State that has implemented the Prospectus Directive, this communication is only addressed to and directed at qualified investors in that Member State within the meaning of the Prospectus Directive. The term “Prospectus Directive” means Directive 2003/71/EC (and amendments thereto, including Directive 2010/73/EU, to the extent implemented in each relevant Member State), together with any relevant implementing measure in the relevant Member State.

For readers in the United Kingdom

This communication, in so far as it constitutes an invitation or inducement to enter into investment activity (within the meaning of s21 Financial Services and Markets Act 2000 as amended) in connection with the securities which are the subject of the offering described in this press release or otherwise, is being directed only at (i) persons who are outside the United Kingdom or (ii) persons who have professional experience in matters relating to investments who fall within Article 19(5) (“Investment professionals”) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the “Order”) or (iii) certain high value persons and entities who fall within Article 49(2)(a) to (d) (“High net worth companies, unincorporated associations etc”) of the Order; or (iv) any other person to whom it may lawfully be communicated (all such persons in (i) to (iv) together being referred to as “relevant persons”). The ADSs are only available to, and any invitation, offer or agreement to subscribe, purchase or otherwise acquire such ADSs will be engaged in only with, relevant persons. Any person who is not a relevant person should not act or rely on this document or any of its contents.
About GW Pharmaceuticals plc

Founded in 1998, GW is a biopharmaceutical company focused on discovering, developing and commercializing novel therapeutics from its proprietary cannabinoid product platform in a broad range of disease areas. GW is advancing an orphan drug program in the field of childhood-onset epilepsy with a focus on Epidiolex® (cannabidiol), which is in Phase 3 clinical development for the treatment of Dravet syndrome, LGS and Tuberous Sclerosis Complex. GW successfully developed the world’s first plant-derived cannabinoid prescription drug, Sativex®, which is approved for the treatment of spasticity due to multiple sclerosis in 28 countries outside the United States. GW has a deep pipeline of additional cannabinoid product candidates which includes compounds in Phase 1 and 2 trials for glioma, schizophrenia and epilepsy.

Forward-looking statements

This news release may contain forward-looking statements that reflect GW’s current expectations regarding future events, including statements regarding the therapeutic benefit, safety profile and commercial value of the Company’s investigational drug Epidiolex, the development and commercialization of Epidiolex, plans and objectives for product development, plans and objectives for present and future clinical trials and results of such trials, plans and objectives for regulatory submissions and approvals. Forward-looking statements involve risks and uncertainties. Actual events could differ materially from those projected herein and depend on a number of factors, including (inter alia), the success of GW’s research strategies, the applicability of the discoveries made therein, the successful and timely completion of uncertainties related to the regulatory process, and the acceptance of Sativex, Epidiolex, if approved, and other products which we may commercialize by consumers and medical professionals. A further list and description of risks, uncertainties and other risks associated with an investment in GW can be found in GW’s filings with the U.S. Securities and Exchange Commission. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. GW undertakes no obligation to update or revise the information contained in this press release, whether as a result of new information, future events or circumstances or otherwise.

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