Phytanix

July 29, 2024

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Industry and Market Data

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DISCLAIMERS

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DISCLAIMERS

Participants in the Solicitation

CBRG, Phytanix and their respective directors and executive officers may be deemed under SEC rules to be participants in the solicitation of proxies of CBRG's stockholders in connection with the Transaction. Investors and security holders may obtain more detailed information regarding the names and interests of CBRG's directors and officers in the Transaction in CBRG's filings with the SEC, including CBRG's Annual Report. Information regarding the persons who may, under SEC rules, be deemed participants in the solicitation of proxies of CBRG's stockholders in connection with the Transaction will be set forth in the proxy statement/prospectus contained in the registration statement on Form S-4 for the Transaction.

Additional Information and Where to Find It

Phytanix intends to file with the SEC a registration statement on Form S-4 that will include a preliminary proxy statement/prospectus to be distributed to stockholders of CBRG in connection with CBRG's solicitation of proxies for the vote by its stockholders with respect to the Transaction. After the registration statement has been filed and declared effective by the SEC, CBRG will mail the definitive proxy statement/prospectus to all CBRG stockholders as of a record date to be established for voting on the Transaction and other matters as may be described in the registration statement. CBRG and Phytanix also will file other documents regarding the Transaction with the SEC. Before making any voting decision, investors and security holders of CBRG are urged to carefully read the entire registration statement, the proxy statement/prospectus and all other relevant documents filed or that will be filed with the SEC, as well as any amendments or supplements to these documents, in connection with the Transaction as they become available because they will contain important information about the proposed Transaction. Investors and security holders will be able to obtain free copies of the registration statement, proxy statement/prospectus and all other relevant documents filed or that will be filed with the SEC by CBRG or Phytanix through the website maintained by the SEC at www.sec.gov. In addition, the documents filed by CBRG may be obtained free of charge by written request to CBRG at 8 the Green, #17538, Dover Delaware, Attention: CEO.

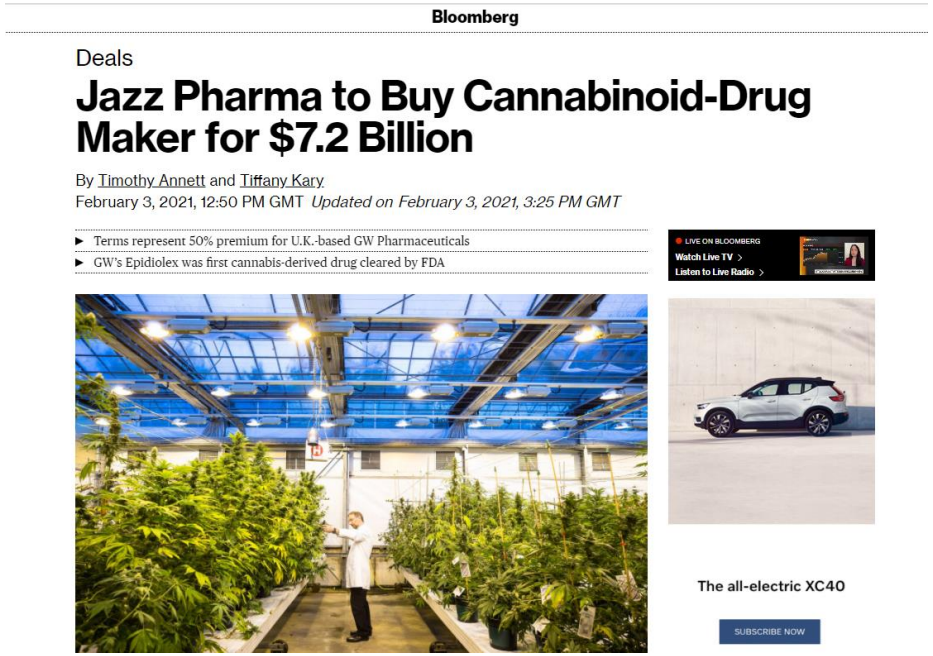
CANNABINOID & CANNABIS-BASED PHARMACEUTICALS: Market Opportunity

Phytanix

- **The development of cannabinoid medicines offers the potential for high return on investment**
- **GW Pharma acquired by Jazz Pharmaceuticals for US $7.2 Billion[1]**
  - Epidiolex (DS, LGS & TSC indication – orphan epilepsy indications
  - Sativex (not approved in the USA; approved in Europe)
- **Cannabinoids ARE approvable as medicines by FDA & Other International Regulators**
  - Marinol®, Nabilone®, Epidiolex®, Sativex®; Syndros®
- **Cannabinoid Market Size is potentially very large**

  1) Pharmaceuticals (Human & Veterinary)
  - The global cannabis pharmaceuticals market size was estimated at **$1.69 billion USD in 2023** and is projected to grow at a compound annual growth rate (CAGR) of 32.6% from 2024 to 2030.[2]

  2) Cosmetic ingredients
  - Ingredients may be sold with appropriate approval
  - Exploitation of the sector comes down to:
    - Regulatory approval
    - Cost of Goods
    - IP protection



Bloomberg

Deals

Jazz Pharma to Buy Cannabinoid-Drug Maker for $7.2 Billion

By Timothy Annett and Tiffany Kary
February 3, 2021, 12:50 PM GMT *Updated on February 3, 2021, 3:25 PM GMT*

- Terms represent 50% premium for U.K.-based GW Pharmaceuticals
- GW's Epidiolex was first cannabis-derived drug cleared by FDA

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1. https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-completes-acquisition-gw-pharmaceuticals#:~:text=DUBLIN%20%2C%20May%205%2C%202021%20%2F,of%20cannabinoid%2Dbased%20prescription%20medicines.
2. https://www.grandviewresearch.com/industry-analysis/cannabis-pharmaceuticals-market

SCIENTIFIC TEAM

Phytanix

Colin Stott - Chief Operating Officer

- Medicinal & Pharmaceutical Chemist / Preclinical & Clinical Development Specialist
- 19 years with GW Pharma as R & D Operations Director (17 years) and latterly Scientific Affairs Director (International Division, 2 years)
- Intimately involved in the invention and development of both **Sativex® (THC/CBD) and Epidiolex® (CBD)**
- Unrivalled knowledge of how to develop high value cannabinoid medicines

Dominic Schiller – Chief IP Counsel

- Dominic is a qualified European Patent Attorney
- 19 years as external IP counsel to GW Pharma
- Provided strategic direction, created and managed GW Pharma's IP portfolio
- Big Pharma work with GSK, Compass Pathways and advisor to several investment funds

Guy Webber – Preclinical Development Director

- Vastly experienced Drug Metabolism and Pharmacokinetic (DMPK) scientist, who has worked in drug metabolism for over 25 years in both contract research and with pharmaceutical companies.
- He is an expert in Absorption, Distribution, Metabolism and Excretion (ADME) and the potential for Drug-Drug Interactions (DDIs) of pharmaceutical medicines, particularly with regard to cannabinoid medicines.
- Former ADME Projects Manager at GW Pharmaceuticals (now Jazz Pharmaceuticals), and has worked in the area of cannabinoid medicines for more than 15 years, and, as a contractor, was closely involved in the ADME evaluation of both Sativex® and Epidiolex®.

Dr. Tamás Bíró – Scientific Advisor

- Dr. Tamás Bíró is a world expert in cannabinoids and the skin
- He is a co-author on GW Pharma’s dermatology patents with Colin Stott and Dr. Vincenzo di Marzo
- He is the former Professor and Chair of the Department of Immunology at the University of Debrecen in Hungary and former Head of the DE-MTA Lendület Cellular Physiology Group of the Hungarian Academy of Sciences located at the Department of Physiology at University of Debrecen.
- Former Director of Applied Resaearch at Phytecs Inc.

PHYTANIX'S THERAPEUTIC AREAS OF FOCUS:

Phytanix

INDICATION 1

TREATMENT OF BLADDER PAIN SYNDROME (PAIN & URINARY SYMPTOMS)

DEVELOPMENT OF A "SIMPLIFIED"CANNABIS EXTRACT (akin to SATIVEX®)

DEVELOP AS PER FDA & EMA GUIDANCE (akin to SATIVEX®)

INDICATION 2

TREATMENT OF TREATMENT-RESISTANT FOCAL SEIZURES IN ADULTS (SEIZURES)

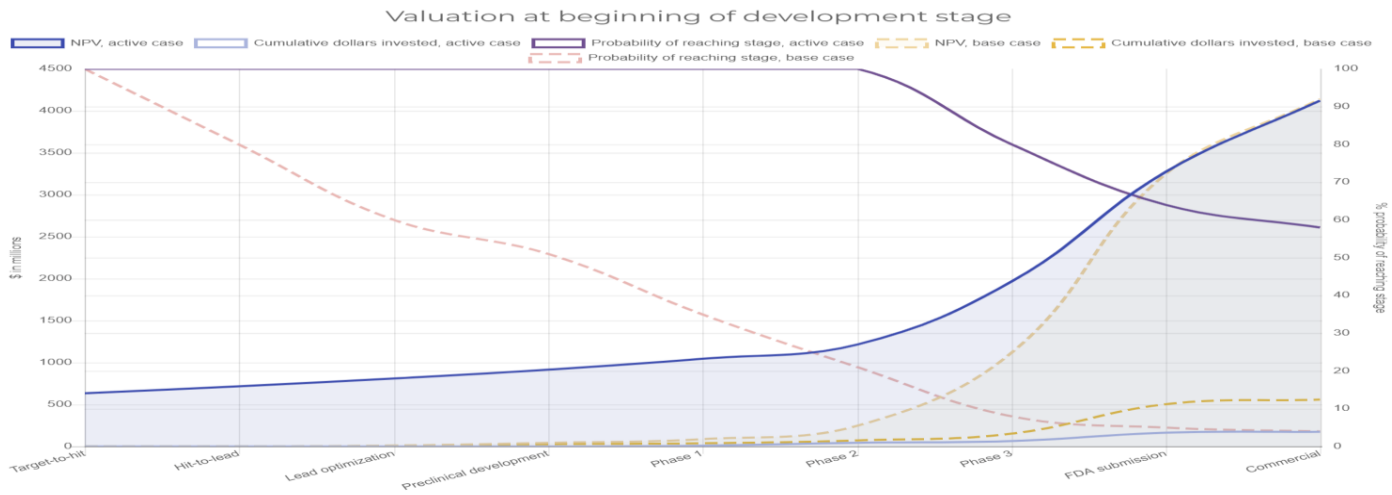
DEVELOPMENT OF A CHEMICALLY SYNTHESIZED STILBENOID *NEW CHEMICAL ENTITY (with potential for 20 year patent life)

DEVELOP AS PER FDA & EMA GUIDANCE (akin to EPIDIOLEX®)

BLADDER PAIN SYNDROME (BPS) INDICATION:
Estimated Project Specific Costs Through Development Lifecycle

Phytanix

Bladder Pain Syndrome (BPS) Indication



Indication	Value at LAUNCH (US $ Billions)
PBS	$4.123

Assumptions:

1) Only 1 Ph 1 study required to progress to Ph2 – others to be conducted in parallel with Ph 2 & Ph 3
2) Assume only 1 Ph 2 study required before progression to Ph 3
3) Assume Ph 3 will be conducted with Licensing Partner

Value at start of program	Value at start of Phase 1	Value at start of Phase 2	Value at start of Phase 3
$635M	$1,046M	$1,217M	$1,968M
Probability of FDA approval: 58%	Probability of FDA approval: 58%	Probability of FDA approval: 58%	Probability of FDA approval: 72%
Investment required for approval: $175M	Investment required for approval: $165M	Investment required for approval: $130M	Investment required for approval: $110M

Project Specific Direct Costs to Start of Phase 1 — ~$7.1M USD; 15 Months

Major Inflexion Point 1

Project Specific Direct Costs to Start of Phase 2 — ~ $9.0M USD; 21 Months

Major Inflexion Point 2

Project Specific Direct Costs to Start of Phase 3 — ~ $16.8M USD; 36+ Months

Major Inflexion Point 3

Amended from: Valuing drugs and biotech companies (baybridgebio.com)

RATIONALE FOR SELECTION OF BPS INDICATION: Commercial Rationale

Phytanix

1) Large potential market

- 3 to 8 million women in the United States may have IC - That is about 3 to 6% of ALL WOMEN in the US[1]
- 1 to 4 million men may have IC too[1]

2) There are very few FDA approved treatments for Bladder Pain Syndrome (BPS) / Interstitial cystitis (IC)

- The last oral medication was ELMIRON® in 1996[2];
- before that it was RIMSO-50 ® (1978)[3]

3) ELMIRON® Price

- Elmiron still sells for $11.99 USD per 100mg capsule[4]
- The recommended dose of ELMIRON® is 300 mg/day taken as one 100 mg capsule orally three times daily[5]
- Annual cost >$13,000 per patient per year.[4]

4) There remains a high unmet medical need

- ELMIRON® causes macular issues (Vision dimming, Difficulty reading, Difficulty adjusting to low light)[5]
- There are now ELMIRON® lawsuits emerging across the USA[6]

5) Cannabinoid clinical trials (with Sativex®) have shown benefit in:

- Randomised, controlled clinical trials of neuropathic pain[7, 8, 9]
- Randomised, controlled clinical trials of bladder dysfunction[10]

1. Interstitial Cystitis Association Website: [https://www.ichelp.org/understanding-ic/learn-about-ic/who-gets-ic/)
2. FDA Website: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=1784
3. https://onlinelibrary.wiley.com/doi/epdf/10.1111/iju.14505
4. https://www.drugs.com/price-guide/elmiron
5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020193s014lbl.pdf
6. https://www.lawsuit-information-center.com/elmiron-lawsuit-update.html
7. Rog et al. 2005
8. Nurmikko et al. 2007
9. Berman et al. 2004
10. Kavia et al. 2010

RATIONALE FOR SELECTION OF BPS INDICATION: Preclinical Rationale (1)

Phytanix

- Cannabinoid receptors are found in the bladder[1]
- Cannabinoid receptor expression in the bladder is altered in bladder overactivity[2]
- CB1 Knockout mice have a higher urinary frequency and more spontaneous activity than normal (Wild Type (WT)) mice[3]
- In vitro, CBD Botanical Extract (containing approx. 4% THC) reduced bladder contractility in rat and human tissue[4]
- In vitro, a number of phytocannabinoids (CBD, CBDV, CBG, THCV but not CBC) reduced bladder contractility in mouse tissue[5]

1. Tyagi et al. 2009. Differential expression of functional cannabinoid receptors in human bladder detrusor and urothelium. J Urol. 2009 Apr;181(4):1932-8.
2. Bakali, E., McDonald, J., Elliott, R.A. et al. 2016. Cannabinoid receptor expression in the bladder is altered in detrusor overactivity. Int Urogynecol J 27, 129–139 (2016).
3. Fullhase et al. 2013. Bladder function in a cannabinoid receptor type 1 knockout mouse. BJU International, 113(1), 144-151. https://doi.org/10.1111/bju.12350
4. Capasso et al. 2011. Inhibitory Effect of Standardized Cannabis sativa Extract and Its Ingredient Cannabidiol on Rat and Human Bladder Contractility. Urology 77(4):1006.e9-1006.e15
5. Pagano et al. 2015. Effect of Non-psychotropic Plant-derived Cannabinoids on Bladder Contractility: Focus on Cannabigerol. Nat Prod Commun. Jun;10(6):1009-1012.

RATIONALE FOR SELECTION OF BPS INDICATION: Preclinical Rationale (2)

Phytanix

- In vivo a CB1 & CB2 receptor agonist CP55,940 increased the micturition (urinary) interval by 46% and threshold pressure by 124%[1]
- In vivo, a non-selective cannabinoid agonist significantly reduced the afferent nerve activity in mice with Cyclophosphamide (CYP)-induced inflamed bladders at bladder pressures above 20 mmHg[2]
- In vivo, administration of a non-selective cannabinoid receptor agonist (10 mg/kg Ajulemic acid) significantly suppressed CYP-induced urinary frequency, as evidenced by the increase in the Inter-contraction Interval[3]
- CB2 agonist (JWH-133) activated CB2 receptors and decreased severity of CYP-induced cystitis and reduced bladder inflammation in mice[4]

1. Gratske et al. 2009. Distribution and function of cannabinoid receptors 1 and 2 in the rat, monkey and human bladder. J Urol. 2009 Apr;181(4):1939-48. doi: 10.1016/j.juro.2008.11.079. Epub 2009 Feb 23.
2. Walczak & Cervero 2011. Local activation of cannabinoid CB1 receptors in the urinary bladder reduces the inflammation-induced sensitization of bladder afferents. Mol Pain. 2011 May 9;7:31. doi: 10.1186/1744-8069-7-31
3. Hiragata et al. 2007. Effects of IP-751, ajulemic acid on bladder overactivity induced by bladder irritation in rats. Urology. 2007 Jul;70(1):202-8.
4. Liu et al. 2020. Cannabinoid receptor 2 activation decreases severity of cyclophosphamide-induced cystitis via regulating autophagy. Neurourol Urodyn. 2020 Jan;39(1):158-169.

RATIONALE FOR SELECTION OF BPS INDICATION: Clinical Rationale
Randomized Controlled Clinical Trial (RCT) Pain Data

Phytanix

Anaesthesia, 2004, **59**, pages 440–452

Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies

William Notcutt,[1] Mario Price,[2] Roy Miller,[3] Samantha Newport,[4] Cheryl Phillips,[4] Susan Simmons[5] and Cathy Sansom[5]

1 Consultant Anaesthetist, 2 Senior Pharmacist, 3 Specialist Registrar, Anaesthesia, 4 Research Assistant, 5 Registered Nurse, Department of Anaesthesia, James Paget Hospital, Lowestoft Road, Great Yarmouth Norfolk NR 31 6LA UK

Clinical Rehabilitation 2003; **17**: 21–29

A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms

Derick T Wade Oxford Centre for Enablement, **Philip Robson** Oxford University Department of Psychiatry, Warneford Hospital, **Heather House, Petra Makela** and **Julia Aram** Oxford Centre for Enablement, Windmill Road, Oxford, UK

Received 23rd August 2002; manuscript accepted 15th September 2002.

Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis

David J. Rog, BMBS; Turo J. Nurmikko, PhD; Tim Friede, PhD; and Carolyn A. Young, MD

NEUROLOGY 2005;65:812–819

Pain 133 (2007) 210–220

PAIN

www.elsevier.com/locate/pain

Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

Turo J. Nurmikko [a,*], Mick G. Serpell [b], Barbara Hoggart [c], Peter J. Toomey [d], Bart J. Morlion [e], Derek Haines [f]

[a] *Division of Neurological Science, University of Liverpool, Liverpool, United Kingdom*
[b] *Gartnavel General Hospital, Glasgow, United Kingdom*
[c] *Solihull Hospital, Birmingham, United Kingdom*
[d] *York District Hospital, York, United Kingdom*
[e] *University Hospital, Leuven, Belgium*
[f] *Castle Hill Hospital, Hull, United Kingdom*

Received 11 March 2007; received in revised form 21 August 2007; accepted 21 August 2007

RATIONALE FOR SELECTION OF BPS INDICATION: RCT Pain Data

Phytanix

Rheumatology 2006;45:50–52
Advance Access publication 9 November 2005
doi:10.1093/rheumatology/kei183

Concise Report

Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis

D. R. Blake, P. Robson[1], M. Ho[2], R. W. Jubb[3] and C. S. McCabe

Objectives. To assess the efficacy of a cannabis-based medicine (CBM) in the treatment of pain due to rheumatoid arthritis (RA).

Pain 112 (2004) 299–306
PAIN
www.elsevier.com/locate/pain

Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial

Jonathan S. Berman[a,*], Catherine Symonds[b], Rolfe Birch[a]

[a]*Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex HA7 4LP, UK*
[b]*GW Pharma Ltd, Porton Down Science Park, Salisbury, Wiltshire SP4 0JQ, UK*

Received 3 November 2003; received in revised form 5 September 2004; accepted 13 September 2004

J Neurol
DOI 10.1007/s00415-012-6739-4

ORIGINAL COMMUNICATION

A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis

R. M. Langford · J. Mares · A. Novotna · M. Vachova · I. Novakova · W. Notcutt · S. Ratcliffe

Received: 16 August 2012 / Revised: 17 October 2012 / Accepted: 29 October 2012
© Springer-Verlag Berlin Heidelberg 2012

EJP
European Journal of Pain

ORIGINAL ARTICLE

A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment

M. Serpell[1], S. Ratcliffe[2], J. Hovorka[3], M. Schofield[4], L. Taylor[5], H. Lauder[5], E. Ehler[6]

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Vol. 39 No. 2 February 2010 *Journal of Pain and Symptom Management* 167

Original Article

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain

Jeremy R. Johnson, MB ChB, Mary Burnell-Nugent, MB BChir, Dominique Lossignol, MB ChB, MRCG, DRCOG, Elena Doina Ganae-Motan, MD, Richard Potts, BSc (Hons), MICR, and Marie T. Fallon, MB ChB, MD, FRCP (E), FRCP (Glasg)
Severn Hospice (J.R.J.), Shrewsbury, Shropshire, and St. Luke's Hospice (M.B.-N.), Turnchapel, Plymouth, United Kingdom; Association Hospitaliere De Brussels (D.L.), Centre des Tumeurs de l'ULB, Brussels, Belgium; Emergency Department (E.D.G.-M.), Hospital "Sf. Ioan cel Nou," Suceava, Romania; GW Pharma Ltd. (R.P.), Ely, Cambridgeshire; and Edinburgh Cancer Research Centre (M.T.F.), University of Edinburgh, Edinburgh, United Kingdom

RATIONALE FOR SELECTION OF BLADDER PAIN SYNDROME INDICATION
Clinical Rationale:

Phytanix

1. An open-label study of Sativex and THC Extract demonstrated activity after 8 weeks treatment in MS patients with bladder dysfunction

- Patients took extracts containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg of each per spray) for eight weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks, and then into a long-term extension.
- 21 patients were recruited and data from 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment (P <0.05, Wilcoxon's signed rank test). However, daily total voided, catheterized and urinary incontinence pad weights also decreased significantly on both extracts. Patient self-assessment of pain, spasticity and quality of sleep improved significantly (P <0.05, Wilcoxon's signed rank test) with pain improvement continuing up to median of 35 weeks.
- Brady et al. 2004. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Mult Scler. 2004; 10: 425-433

2. A randomised, double-blind, placebo controlled clinical trial Sativex in 135 MS patients

- **Sativex produced statistically significant decrease from baseline in a number of urinary parameters**
- Sativex produced statistically significant decrease from baseline in Total number of voids per 24 hours, Number of daytime voids, Number of episodes of nocturia, bladder symptom severity and patient global impression of change (after 8 weeks)
- Kavia et al. 2010. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Mult Scler. 2010 Nov;16(11):1349-59.

3. A randomised, double-blind, placebo controlled clinical trial (CAMS-LUTS study) of cannabis extract and THC in 630 MS patients

- **A cannabis extract and THC produced statistically significant decrease from baseline in urge incontinence episode rate (after 15 weeks)**
- In the CAMS-LUTS study, 630 MS patients received oral administration of cannabis extract, Delta(9)-tetrahydrocannabinol (THC) or matched placebo.
- All three groups showed a significant reduction, p<0.01, in adjusted urge incontinence episode rate from baseline to the end of treatment: cannabis extract, 38%; THC, 33%; and placebo, 18%. Both active treatments showed significant effects over placebo (cannabis extract, p=0.005; THC, p=0.039).
- Freeman et al. 2006. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). Int Urogynecol J Pelvic Floor Dysfunct. 2006; 17: 636-641.

4. Survey of BPS / IC patients by Dr. Mary Lynch and team suggested that cannabis was effective in patients with BPS / IC.

- Total of n=97 patients surveyed: n=44 were cannabis users, n=53 were non-users (Single Center study)
- **Of the 45 patients who responded to the question as to whether cannabis was effective, 37 said it was slightly effective or better (82%): 36% (Slightly Effective); 36% Effective, 11% Very Effective**
- Of the 48 patients who responded to the “Negative Side Effects” question: 60% said they had none. [27% mild, 6% moderate, 6% severe side effects]
- Of the 44 patients who responded to the question about any medication changes: 61% reported no change, 27% reported a decrease in medication and 18% discontinued medication. No-one reported an increase in medication.

RATIONALE FOR SELECTION OF BPS INDICATION: Randomised, Controlled Trials (RCTs) - Bladder Data

Phytanix

SATIVEX has already shown to be effective in an RCT of Bladder Dysfunction (Kavia et al. 2010)

Research Paper

Multiple Sclerosis

Multiple Sclerosis
16(11) 1349–1359
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msj.sagepub.com
SAGE

Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis

RBC Kavia[1], D De Ridder[2], CS Constantinescu[3], CG Stott[4] and CJ Fowler[1]

Abstract

Background: Bladder dysfunction is a common feature of multiple sclerosis (MS).

Objective: In this study we aimed to assess the efficacy, tolerability and safety of Sativex® (nabiximols) as an add-on therapy in alleviating bladder symptoms in patients with MS.

Methods: We undertook a 10-week, double-blind, randomized, placebo-controlled, parallel-group trial in 135 randomized subjects with MS and overactive bladder (OAB).

Results: The primary endpoint was the reduction in daily number of urinary incontinence episodes from baseline to end of treatment (8 weeks). Other endpoints included incidence of nocturia and urgency, overall bladder condition (OBC), daytime frequency, Incontinence Quality of Life (I-QOL), Patient's Global Impression of Change (PGIC) and volume voided. The primary endpoint showed little difference between Sativex and placebo. Four out of seven secondary endpoints were significantly in favour of Sativex: number of episodes of nocturia (adjusted mean difference −0.28, $p = 0.010$), OBC (−1.16, $p = 0.001$), number of voids/day (−0.85, $p = 0.001$) and PGIC ($p = 0.005$). Of the other endpoints, number of daytime voids was statistically significantly in favour of Sativex (−0.57, $p = 0.044$). The improvement in I-QOL was in favour of Sativex but did not reach statistical significance.

Conclusions: Although the primary endpoint did not reach statistical significance, we conclude that Sativex did have some impact on the symptoms of overactive bladder in patients with MS, providing evidence of some improvement in symptoms associated with bladder dysfunction in these subjects.

Keywords
cannabinoid, detrusor overactivity, multiple sclerosis, overactive bladder, Sativex

Date received: 9th October 2009; revised: 19th March 2010; 15th June 2010; accepted: 16th June 2010

Table 3. Efficacy data – change from baseline to end of study

	Mean change from baseline				
	Sativex		Placebo		
Endpoint	*n*	Adjusted Mean	*n*	Adjusted Mean	*p*-value
Daily incontinence episodes	60	−1.08	64	−0.98	0.569
Total number of voids (per 24 h)	60	−1.75	64	−0.9	0.007
Number Daytime voids (per day)	60	−1.23	64	−0.66	0.044
Nocturia episodes (per day)	60	−0.52	64	−0.24	0.01
Void urgency episodes (per day)	60	−1.88	64	−1.12	0.07
Bladder symptom severity (Overall Bladder Condition) NRS	61	−2.21	66	−1.05	0.001
Incontinence QOL	59	14.3	61	10.4	0.166
Patient Global Impression of Change (recorded at end of study)	61	84% improve	67	58% improve	0.005

NRS, numerical rating scale; QOL, quality of life.

All but one of the secondary endpoints were statistically in favour of THC: CBD in this study

INTELLECTUAL PROPERTY PROTECTION FOR BPS INDICATION

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- Dominic Schiller built a robust and effective Intellectual Property position covering Sativex (a cannabis-based medicine made from complex cannabis extracts) used to tread spasticity in MS and Epidiolex (a highly purified CBD) used to treat seizures in Dravet Syndrome (DS), Lennox-Gastaut Syndrome (LGS) and Tuberous Sclerosis Complex (TSC)
- At a minimum, a medicine comprising of a new extract would be entitled to regulatory data exclusivity *
    - 5 years in the USA; 10 years in Europe

  ** Data exclusivity. = Period of time during which an applicant cannot rely on the data in support of another marketing authorisation for the purposes of submitting an application, obtaining marketing authorisation or placing the product on the market (i.e.: generics, hybrids, biosimilars)*
- The same principles apply to the approach we will take for the extract we take into BPS/IC
- We expect to create new IP providing an extended period of protection (potentially up to 25 years in Europe using patents and SPC protection (patent extension based on approval).
- Example of patented plant extracts obtained include:
    - WO2004016277 (Sativex): Link to patent WO2004016277
    - WO2011032502 (Reducose – a mulberry extract for pre-diabetes): Link to patent WO2011032502
- Can protect
    - Extraction methodology (process patent) – here we will look to access to new IP (unpublished from Unified Science)
    - The extract per se (i.e. the composition of the extract) - (argue inventive step based on simplification)
    - Formulation patents (e.g. Nano4m and next generation IP for a modified extract)
    - Medical use patents
        - Support required (e.g. Efficacy data from an in vivo model of BPS / IC (e.g. CYP-induced IC)) – possibly with comparator drug

CANNABIS BASED MEDICINES CAN SUCCESSFULLY GET THROUGH CLINICAL PHASE 1: Single & Multiple Dose Study

Phytanix

Eur J Clin Pharmacol (2013) 69:1135–1147
DOI 10.1007/s00228-012-1441-0

PHARMACOKINETICS AND DISPOSITION

A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray

C. G. Stott · L. White · S. Wright · D. Wilbraham · G. W. Guy

Received: 23 August 2012 / Accepted: 17 October 2012 / Published online: 22 November 2012
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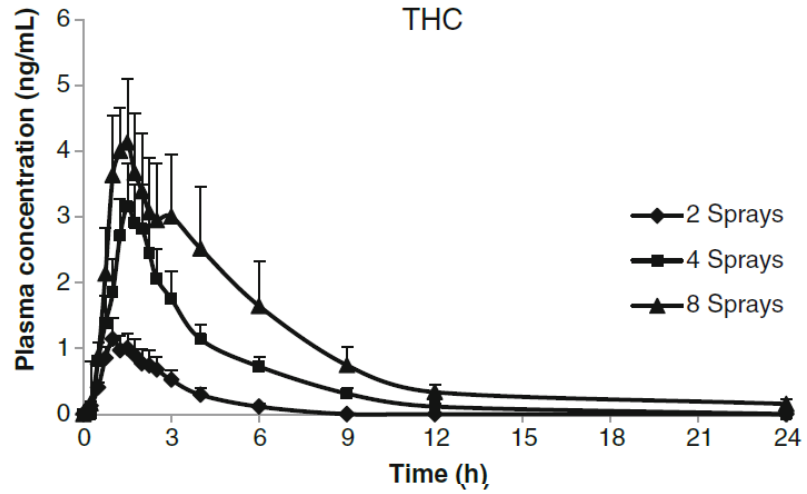
a



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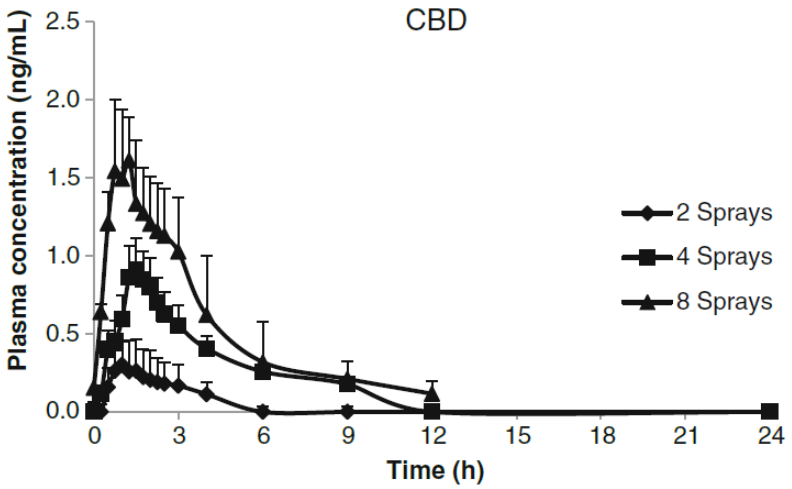

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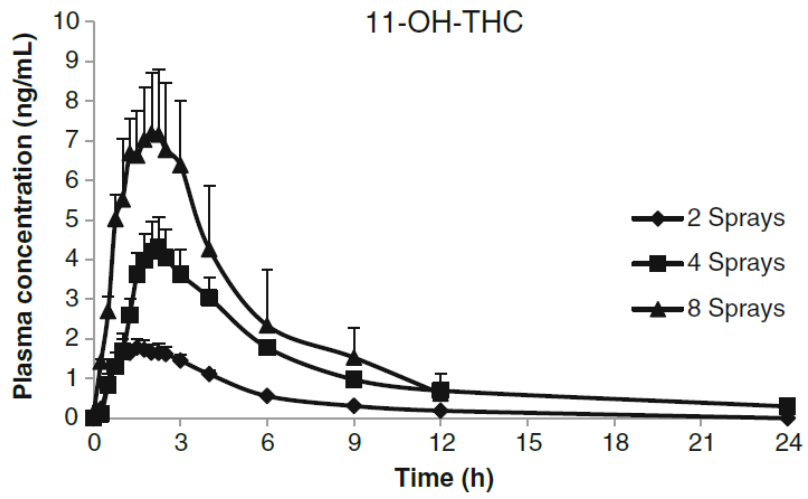

CANNABIS BASED MEDICINES CAN SUCCESSFULLY GET THROUGH CLINICAL PHASE 1: Fed v Fasted Pk Study

Phytanix

Eur J Clin Pharmacol
DOI 10.1007/s00228-012-1393-4

PHARMACOKINETICS AND DISPOSITION

A phase I study to assess the effect of food on the single dose bioavailability of the THC/CBD oromucosal spray

C. G. Stott · L. White · S. Wright · D. Wilbraham · G. W. Guy

Received: 28 August 2012 / Accepted: 28 August 2012
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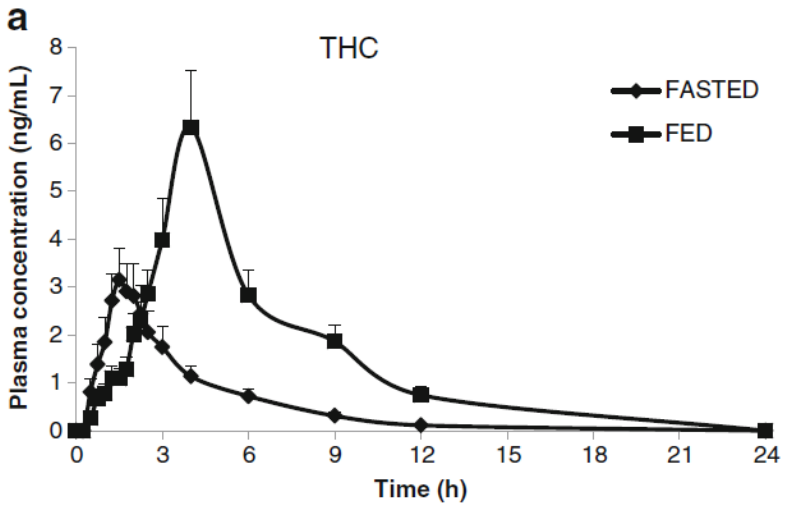

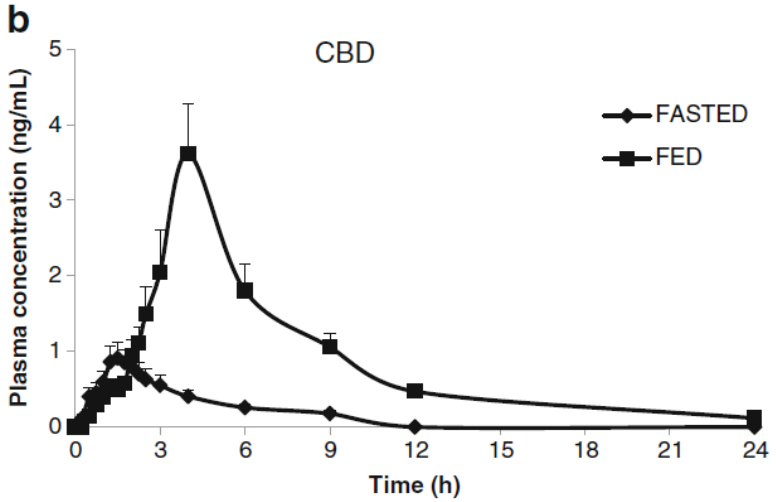

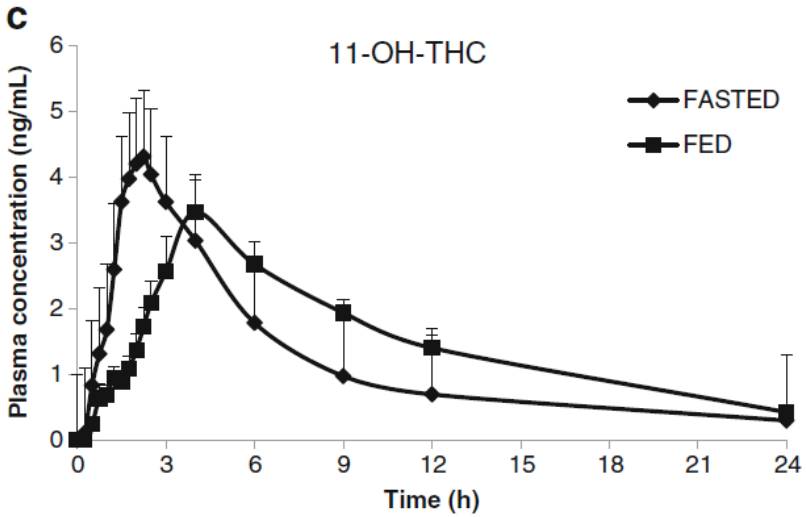

TYPICAL PHARMACEUTICAL DEVELOPMENT TIMELINE:
Time From Project Start To Regualtory Application For Clinical Phase 1

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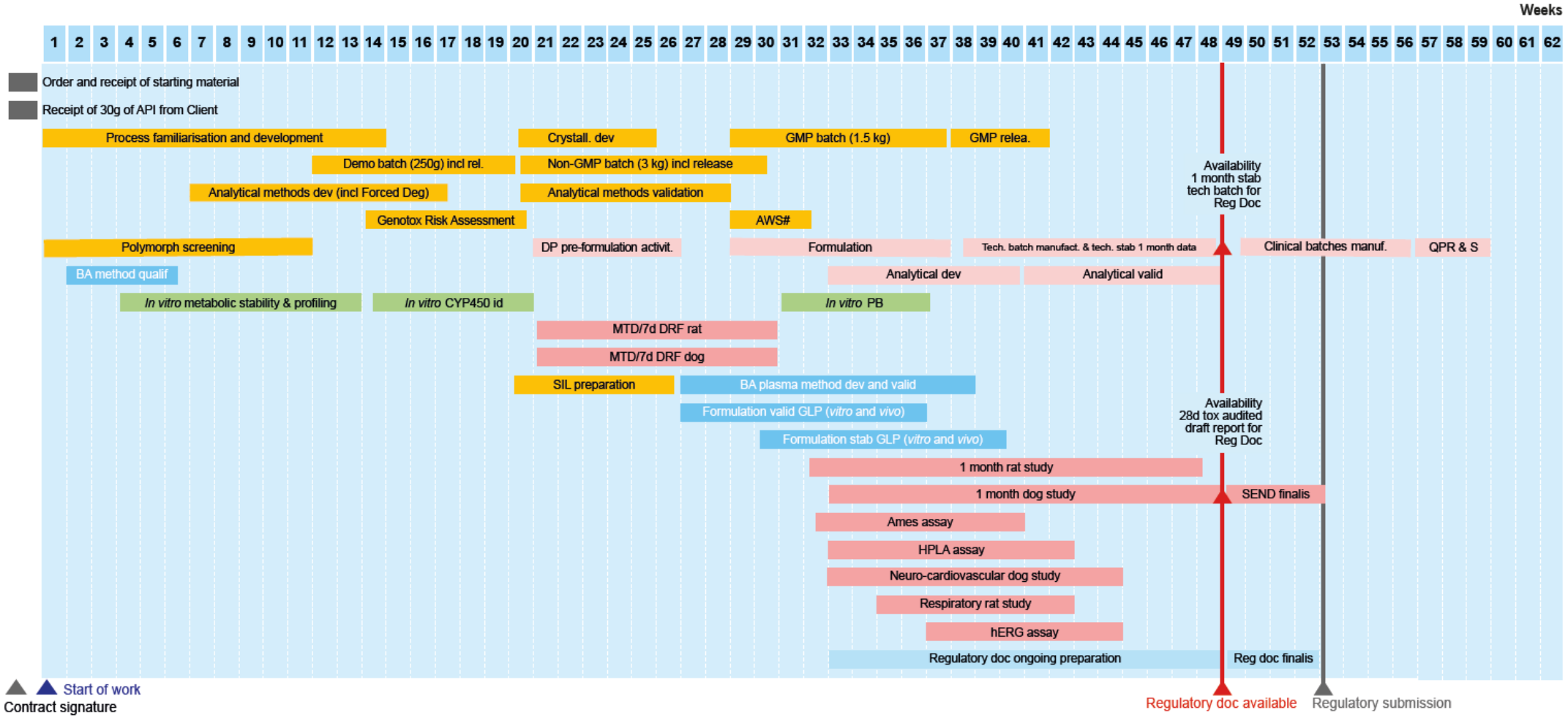

POTENTIAL MANUFACTURING PARTNERS FOR PRODUCT DEVELOPMENT

Phytanix

BPS / IC Project

United Science Holdings (Osceola, Wisconsin)

- Capable of producing Botanical Extracts and Ingredients/ High Purity Isolates
- Cannabinoids, Terpenes, Flavonoids, Alkaloids, Xanthins
- Extraction Equipment (can handle up to 3 Tons/Day Biomass)
- Continuous Manufacturing Operations (Wiped Film Distillation)
- Chromatography Separations (Up to 100Kg / hour): Cannabinoids, Alkaloids
- Formulation & Laboratory Support

Epilepsy Project

curia

Curia (formerly Albany Molecular Research, Inc. (AMRI), NY)

- Well known CDMO – synthesized cannabinoid APIs
- Capable of undertaking Custom API Manufacturing
- Fermentation
- Finished Dosage Forms & Lipid Nanoparticles

Purisys™

Purisys (formerly Noramco Inc. (Wilmington, Delaware)

- Well known CDMO – synthesized cannabinoid APIs
- Specialize in: Process Development, Synthetic Chemistry, Analytical Capabilities, Small Scale Manufacturing, Regulatory Capabilities
- Specialize in Controlled Substance API manufacturing
- Cannabinoid APIs, Psychedelics & Other Controlled Substances

Sterling

Sterling Pharma Solutions (North Carolina, USA; Wisconsin USA; Various locations, UK)

- Full-service API development, scale up and cGMP contract manufacturing services from grams to tonnes
- Support for drug discovery process, from initial screening to lead optimisation
- Analytical services to support the entire molecule lifecycle
- Multidisciplinary approach to early scale-up

POTENTIAL CRO PARTNERS FOR PRECLINICAL / PRODUCT DEVELOPMENT

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(formerly Covance) – UK, Germany, US, Singapore & China locations

- Labcorp did much of the preclinical development for Sativex and all of it for Epidiolex.
- Very experienced in the setup, validation and bioanalysis of cannabinoids in plasma samples from preclinical studies

UK, Germany & USA locations

- Evotec have an integrated platform approach from API availability to Clinical Phase 1 approval

UK location

- Sequani did much of the early preclinical development for Sativex.

Various Locations: UK, USA & China

- Pharmaron did all of the ADME / DMPK for Sativex and Epidiolex (UK)

Various Locations: UK, USA, Canada, France & Netherlands

- Unknown whether Charles River has any experience of developing cannabinoids
- GW Pharma did not use Charles River during the Sativex and Epidiolex developments

TREATMENT-RESISTANT FOCAL SEIZURES IN ADULTS (TRFSA) INDICATION: Estimated Project Specific Costs Through Development Lifecycle

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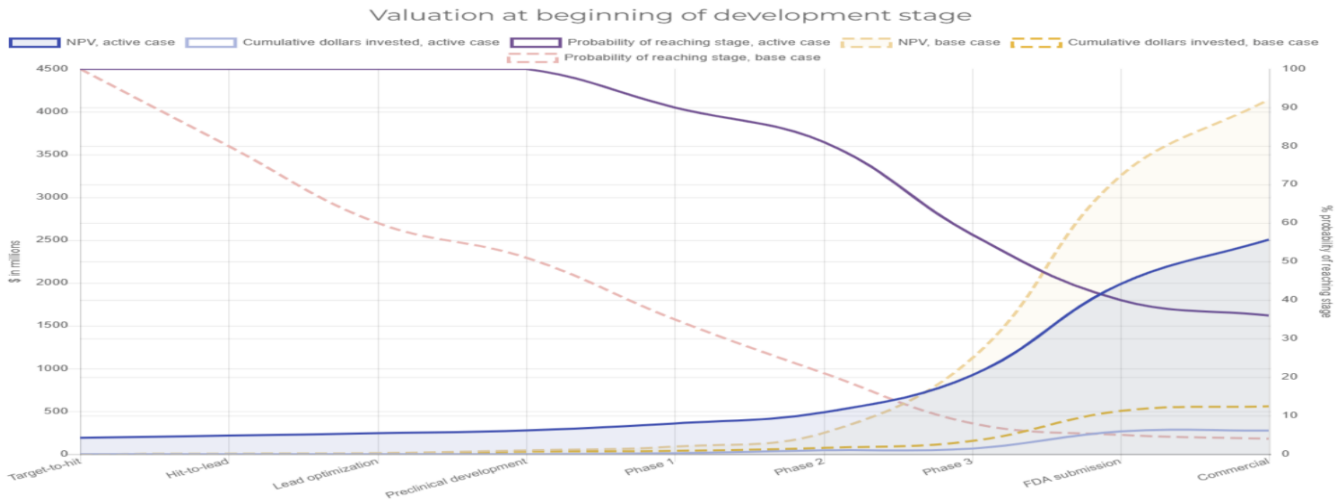
Treatment-Resistant Focal Seizures Indication (TRFS)



Indication	Value at LAUNCH (US $ Billions)
TRFSA	$2.506

Assumptions:

1) Only 1 Ph 1 study required to progress to Ph2 – others to be conducted in parallel with Ph 2 & Ph 3
2) Assume only 1 Ph 2 study required before progression to Ph 3
3) Assume Ph 3 will be conducted with Licensing Partner
4) Assume Ph 2 will take at least 18 months

Value at start of program	Value at start of Phase 1	Value at start of Phase 2	Value at start of Phase 3
$192M	$359M	$489M	$922M
Probability of FDA approval: 36%	Probability of FDA approval: 40%	Probability of FDA approval: 44%	Probability of FDA approval: 63%
Investment required for approval: $275M	Investment required for approval: $265M	Investment required for approval: $230M	Investment required for approval: $210M

Project Specific Direct Costs to Start of Phase 1 — ~$7.5M USD; 15 Months

Major Inflexion Point 1

Project Specific Direct Costs to Start of Phase 2 — ~ $9.0M USD; 21 Months

Major Inflexion Point 2

Project Specific Direct Costs to Start of Phase 3 — ~ $17.2M USD; 36+ Months

Major Inflexion Point 3

Amended from: Valuing drugs and biotech companies (baybridgebio.com)

RATIONALE FOR SELECTION OF TRFSA INDICATION:
Commercial Rationale:

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1) Large potential market

- In a systematic review and meta-analysis of the prevalence and incidence of epilepsy:
  - active generalized epilepsy was found to be the most prevalent (4.33 per 1,000 individuals)[1], while
  - active focal seizures accounted for 2.99 per 1,000 individuals[1]

2) There is a recent precedent with regard to FDA approved treatments for TRFSA

- XCOPRI approved by the FDA in November 2019[2]
- ONTOZRY (European Name for XCOPRI) approved by EMA in March 2021[3]

3) XCOPRI® Price

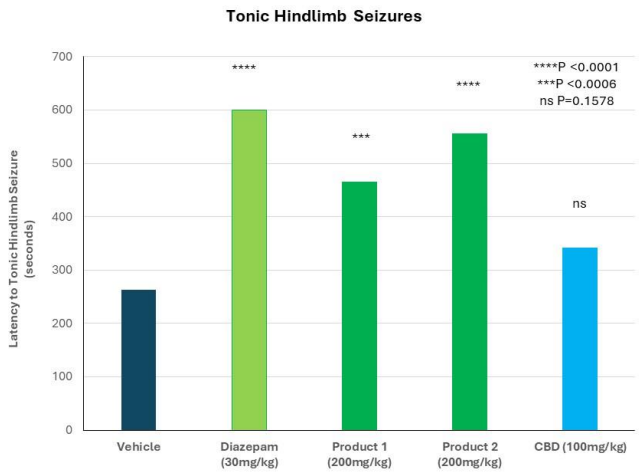
- XCOPRI® sells for more than $14,000 USD per patient per year in the USA[4]

4) There remains a high unmet medical need

- EPIDIOLEX® is approved in its current indications (not include TRFSA) at relatively high doses (10 or 20mg/kg/day)[5]
- It has a sesame oil base and is a 100mg/mL CBD concentration[5]
- Daily adult dose at 20mg/kg/day = approx. 1500mg CBD per day (= 15mL of oily solution)[5]

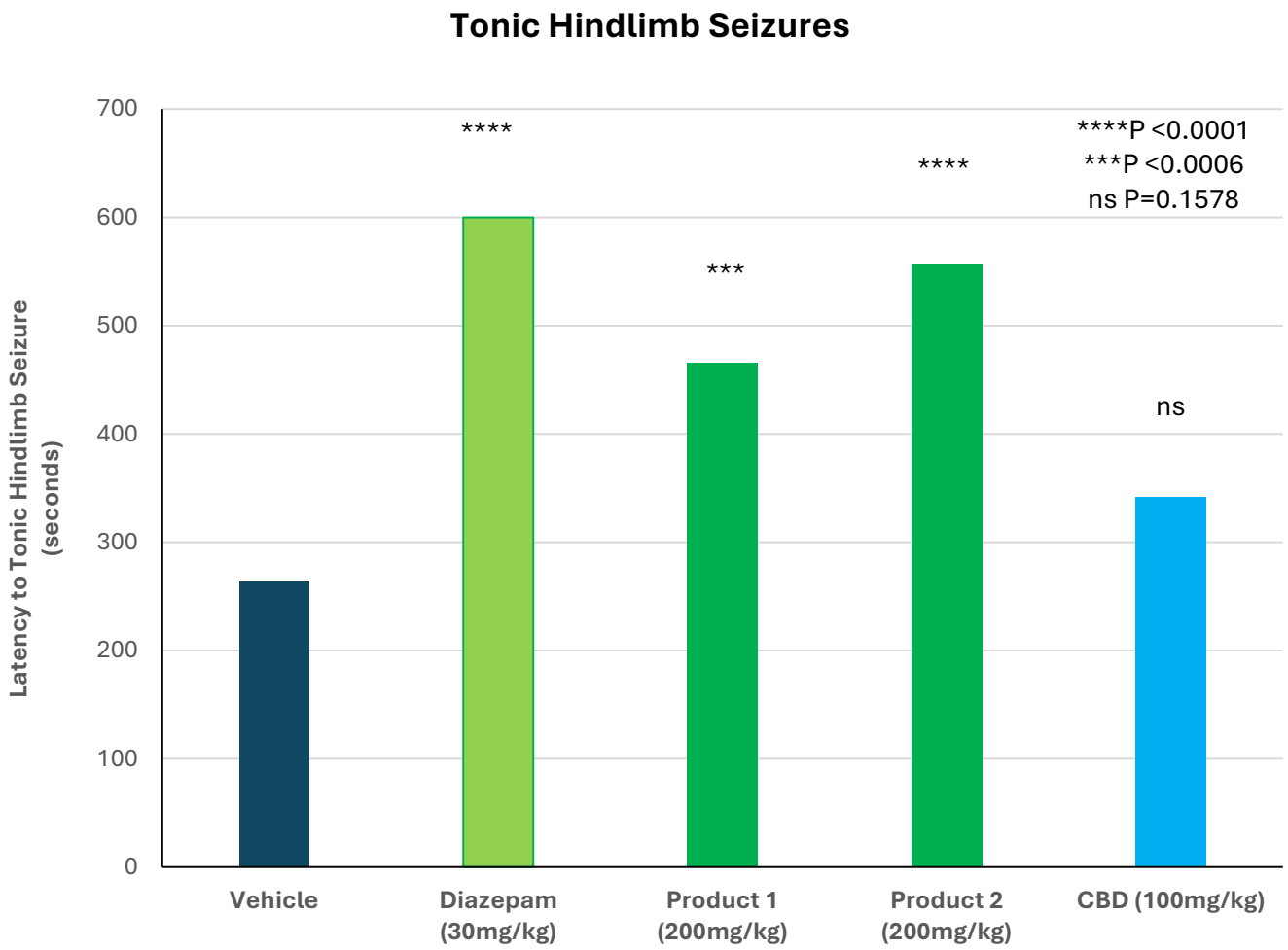
5) PHYTANIX DEVELOPMENT CANDIDATE EFFECTIVE IN IN VIVO MODEL of SEIZURE:

- Similar in vivo model to that used for CBD - To be tested in other models[6]
- Potency / Bioavailability likely to be improved by further modification



1. Fiest et al. 2017 Neurology 2017;88:296–303
2. https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-partial-onset-seizures
3. https://www.ema.europa.eu/en/medicines/human/EPAR/ontozry#:~:text=Ontozry%20received%20a%20marketing%20authorisation,EU%20on%2026%20March%202021.
4. Xcopri Prices, Coupons, Copay & Patient Assistance - Drugs.com
5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210365s015lbl.pdf
6. Phytanix Inc. Data on File

RATIONALE FOR SELECTION OF TRFSA INDICATION:
Preclinical Rationale:



- Product 1 & Product 2 invented by Colin Stott (as Phytotherapeutix Ltd, a UK subsidiary of Phytanix Inc.)
- Patent filed for Products 1 and 2
  - Product 1 has "1st Medical Use" IP
  - Product 2 is a New Chemical Entity
- Similar "next-generation" products in development with view to selecting lead candidate
- Phytanix believes that these and similar products will behave like CBD
  - Possible that such products will have similar wide pharmacology as CBD
  - Possibility to develop for a range of indications including:
    - CNS disorders such as epilepsy, psychosis, depression, neurodegenerative disorders etc.
    - Other disorders: cardioprotection, metabolic disorders etc.

Amended from Published Patent Application No.: US63003270 / WO2021198692(A1)

RATIONALE FOR SELECTION OF TRFSA INDICATION: Clinical Rationale (1)

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CBD IS EFFECTIVE IN MULTIPLE RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL STUDIES OF SEZIURE

The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Authors: Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group* Author Info & Affiliations

Published May 25, 2017 | N Engl J Med 2017;376:2011-2020 | DOI: 10.1056/NEJMoa1611618 | VOL. 376 NO. 21

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome

Orrin Devinsky, M.D., Anup D. Patel, M.D., J. Helen Cross, M.B., Ch.B., Ph.D., Vicente Villanueva, M.D., Ph.D., Elaine C. Wirrell, M.D., Michael Privitera, M.D., Sam M. Greenwood, Ph.D., Claire Roberts, Ph.D., Daniel Checketts, M.Sc., Kevan E. VanLandingham, M.D., Ph.D., and Sameer M. Zuberi, M.B., Ch.B., M.D., for the GWPCARE3 Study Group*

THE LANCET

FULL TEXT ARTICLE

Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial

Elizabeth A Thiele MD, Eric D Marsh MD, Jacqueline A French MD, Maria Mazurkiewicz-Beldzinska MD, Selim R Benbadis MD, Charuta Joshi MBBS, Paul D Lyons MD, Adam Taylor PhD, Claire Roberts PhD and Kenneth Sommerville MD

Lancet, The, 2018-03-17, Volume 391, Issue 10125, Pages 1085-1096, Copyright © 2018 Elsevier Ltd

JAMA Neurology

View Article

JAMA Neurol. 2020 May; 77(5): 1–10.
Published online 2020 Mar 2. doi: 10.1001/jamaneurol.2020.0073: 10.1001/jamaneurol.2020.0073
PMCID: PMC7052786
PMID: 32119035

Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome

A Randomized Clinical Trial

Ian Miller, MD,[✉1] Ingrid E. Scheffer, MBBS, PhD, FRS,[✉2,3,4] Boudewijn Gunning, MD,[5] Rocio Sanchez-Carpintero, MD, PhD,[6] Antonio Gil-Nagel, MD, PhD,[7] M. Scott Perry, MD,[8] Russell P. Saneto, DO, PhD,[9] Daniel Checketts, MSc,[10] Eduardo Dunayevich, MD,[11] and Volker Knappertz, MD[11], for the GWPCARE2 Study Group

JAMA Neurology

View Article

JAMA Neurol. 2021 Mar; 78(3): 1–9.
Published online 2020 Dec 21. doi: 10.1001/jamaneurol.2020.4607: 10.1001/jamaneurol.2020.4607
PMCID: PMC7754080
PMID: 33346789

Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex

A Placebo-Controlled Randomized Clinical Trial

Elizabeth A. Thiele, MD, PhD,[✉1] E. Martina Bebin, MD, MPA,[2] Hari Bhathal, MD,[3] Floor E. Jansen, MD,[4] Katarzyna Kotulska, MD, PhD,[5,6] John A. Lawson, MBBS, PhD,[7] Finbar J. O'Callaghan, MBChB, PhD,[8] Michael Wong, MD, PhD,[9] Farhad Sahebkar, MD,[10] Daniel Checketts, MSc,[11] and Volker Knappertz, MD[10], for the GWPCARE6 Study Group

RATIONALE FOR SELECTION OF TRFSA INDICATION: Clinical Rationale (2)

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Observational Study > Epilepsy Behav. 2023 Jul:144:109210. doi: 10.1016/j.yebeh.2023.109210. Epub 2023 May 15.

Cannabidiol as an adjuvant treatment in adults with drug-resistant focal epilepsy

Silvia Kochen [1], Manuela Villanueva [1], Liliana Bayarres [1], Anilu Daza-Restrepo [1], Silvia Gonzalez Martinez [1], Silvia Oddo [2]

Affiliations + expand

PMID: 37196452 DOI: 10.1016/j.yebeh.2023.109210

Abstract

Cannabidiol oil (CBD) has been approved as an anti-seizure medication for the treatment of uncommon types of epilepsy, occurring in children: Dravet syndrome, Lennox-Gastaut syndrome, and Tuberous Sclerosis Complex. There are few publications in relation to use the CBD in adult patients with focal drug-resistant epilepsy. The objective of this study was to evaluate the efficacy, tolerability, safety, and quality of life, of adjuvant treatment with CBD, in adult patients with drug-resistant focal epilepsy for at least 6 months. An open, observational, prospective cohort study was conducted using a before-after design (time series) in adult patients undergoing outpatient follow-up in a public hospital in Buenos Aires, Argentina. From a total of 44 patients, 5% of patients were seizure-free, 32% of patients reduced more than 80% of their seizures and 87% of patients reduced 50% of their monthly seizures. Eleven percent presented a decrease of less than 50% in seizure frequency. The average final dose was 335 mg/d orally administered. Thirty-four percent of patients reported mild adverse events and no patient reported severe adverse effects. At the end of the study, we found in most patients a significant improvement in the quality of life, in all the items evaluated. Adjuvant treatment with CBD in adult patients with drug-resistant focal epilepsy was effective, safe, well tolerated, and associated with a significant improvement in their quality of life.

Keywords: Adults; Cannabidiol; Drug-resistant epilepsy; Focal epilepsy.

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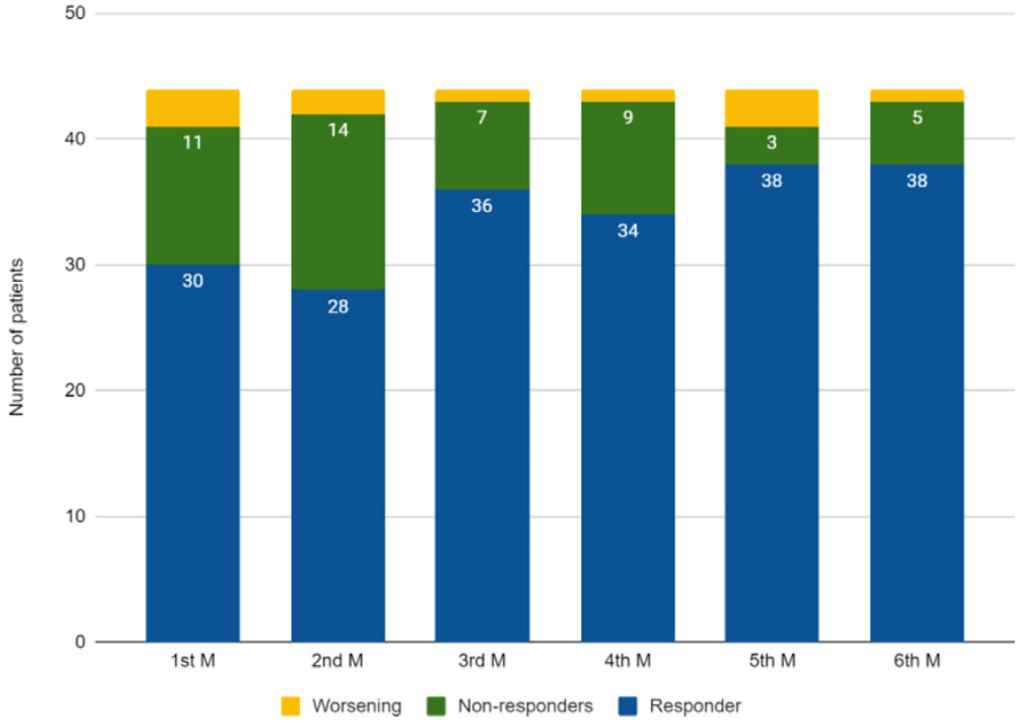
Kochen et al. 2023: CBD as an adjuvant treatment in adults with drug-resistant focal epilepsy



- Worsening (increase number of seizures),
- Non-responders = (decrease number of seizures between 0–50%),
- Responders (decrease number of seizures by 50% or more)

Table 2
Cannabidiol Efficacy.

Efficacy	Patients
Seizure free	2 (5%)
Reduction between 80–99%	14 (32%)
Reduction between 50–79%	22 (50%)
Reduction < 50%	5 (11%)
Increases	1 (2%)

- The initial dose was 250 mg/day.
- The median dose, at the end of the trial was 335 mg/day.
- The subgroup of the 38 responding patients ended with a mean of 329 mg/day.
- 20 patients (53%) completed the trial with a dose of 250 mg/d of CBD
- 12 patients (32%) = 375 mg/day
- 6 patients (16%) = 500 mg/d.
- While patients in the non-responders group had a mean dose of
- 350 mg/day
- The worsening group ended with 500 mg/day of CBD

Jazz Pharmaceuticals: CBD in Focal Seizures : American Epilepsy Society (AES) 2023

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Home / Abstracts

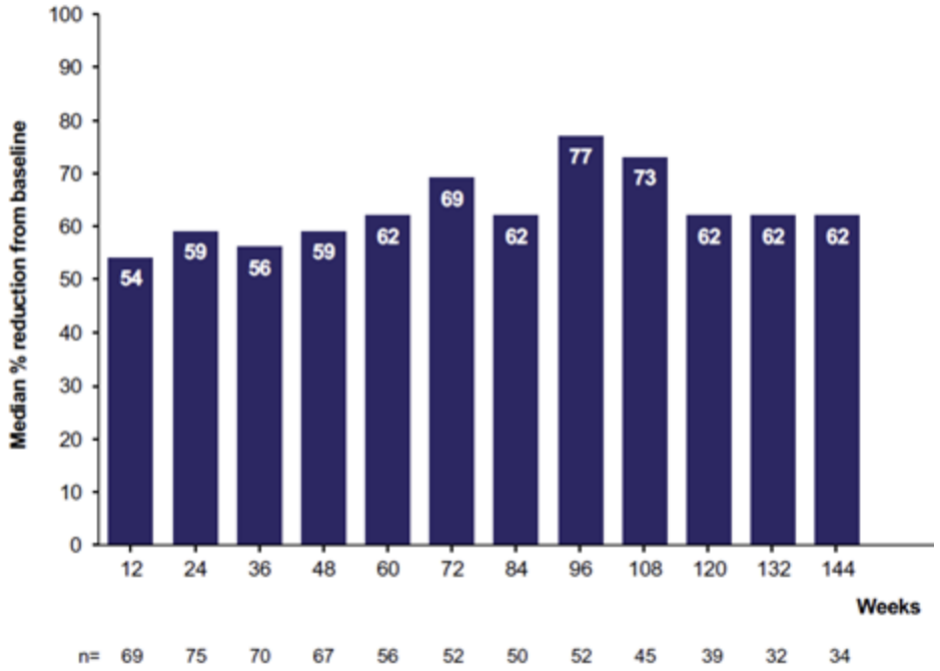
Abstracts

Real-World Outcomes of Cannabidiol (CBD) in Treatment-Resistant Focal Epilepsies: Experience from the Expanded Access Program (EAP)

Abstract number : 2.493
Submission category : 7. Anti-seizure Medications / 7E. Other
Year : 2023
Submission ID : 1382
Source : www.aesnet.org
Presentation date : 12/3/2023 12:00:00 AM
Published date :

Authors :
Presenting Author: Anup D. Patel, MD – Nationwide Children's Hospital

Jerzy P. Szaflarski, MD, PhD – University of Alabama at Birmingham; Elizabeth A. Thiele, MD, PhD – Massachusetts General Hospital; Paul Lyons, MD, PhD – Winchester Neurological Consultants; Michael Boffa, MD – Jazz Pharmaceuticals, Inc., Gentium Spa; Teresa Greco, PhD – Jazz Pharmaceuticals, Inc., Gentium Spa; Timothy Saurer, PhD – Jazz Pharmaceuticals, Inc.; Karthik Rajasekaran, PhD – Jazz Pharmaceuticals, Inc.; Kelly Simontacchi, PhD – Jazz Pharmaceuticals, Inc.



- Effect of CBD (Epidiolex®) in Treatment resistant Focal Seizures
- CBD (Epidiolex®) produces a **62% reduction in focal seizures after 144 weeks of treatment** (Expanded Access Program)
- At least 50% reduction (responder rate) was reported in **51%–72% of patients** for focal seizures at 12-week visit windows through 144 weeks

Park et al. AES 2023: Long-Term Effectiveness of CBD Against Focal-Onset Seizures in Treatment-Resistant Epilepsies (TRE)

Long-term Effectiveness of Cannabidiol (CBD) Against Focal-Onset Seizures in Treatment-Resistant Epilepsies (TRE)

Abstract number : 3.291
Submission category : 7. Anti-seizure Medications / 7E. Other
Year : 2023
Submission ID : 1029
Source : www.aesnet.org
Presentation date : 12/4/2023 12:00:00 AM
Published date :

Authors :
Presenting Author: Yong D. Park, MD – Medical College of Georgia at Augusta University, Department of Neurology, AU Health System, Augusta, GA, USA

Karthik Rajasekaran, PhD – Jazz Pharmaceuticals, Inc, Carlsbad, CA, USA; Teresa Greco, MD, PhD – Jazz Pharmaceuticals, Inc, Gentium Srl, Villa Guardia, Italy; Farhad Sahebkar, MD – Jazz Pharmaceuticals, Inc, Carlsbad, CA, USA; Robert J. Flamini, MD – PANDA Neurology, Atlanta, GA, USA

Park et al. AES 2023: Long-Term Effectiveness of CBD Against Focal-Onset Seizures in Treatment-Resistant Epilepsies (TRE)

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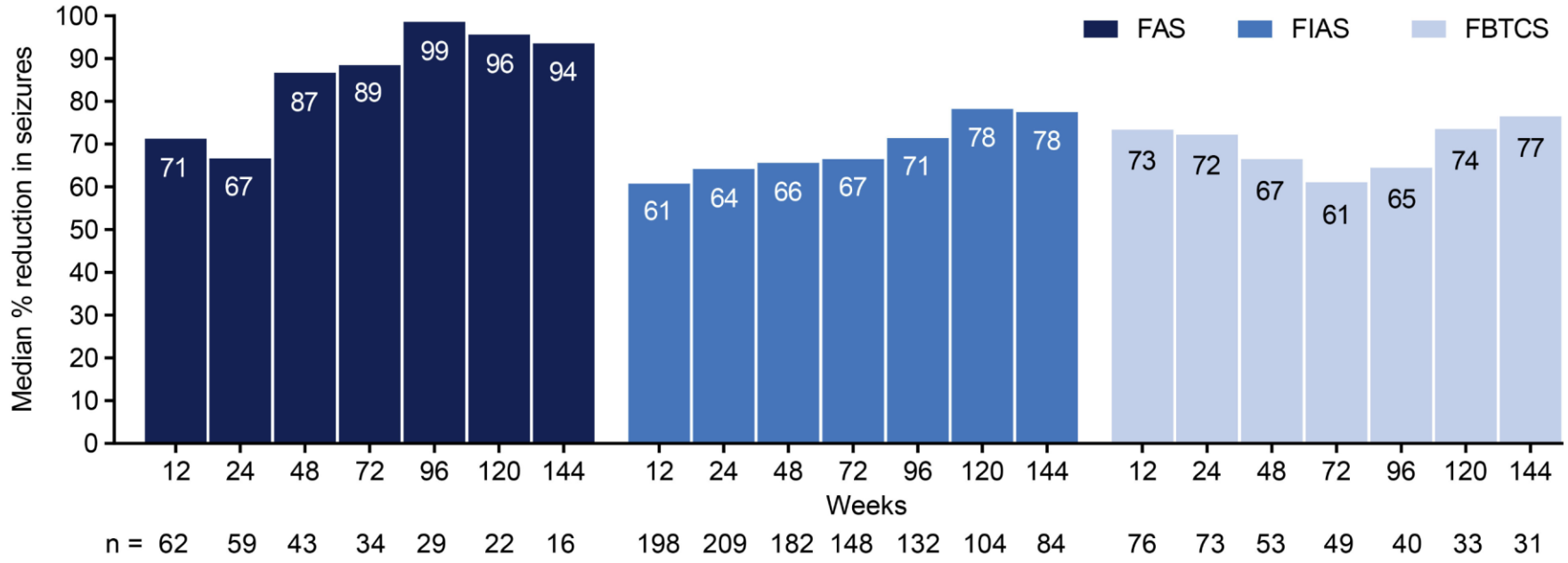
Figure 1. Median percentage reduction from baseline in FAS, FIAS, and FBTSC.



FAS, focal aware seizures; FIAS, focal impaired awareness seizures; FBTCS, focal to bilateral tonic-clonic seizures.

- CBD (Epidiolex®) produces a **94% reduction in Focal Aware Seizures (FAS) after 144 weeks of treatment** (Expanded Access Program)
- CBD (Epidiolex®) produces a **78% reduction in Focal Impaired Awareness Seizures (FIAS) after 144 weeks of treatment** (Expanded Access Program)
- CBD (Epidiolex®) produces a **77% reduction in Focal-to-Bilateral Tonic-Clonic Seizures (FBTCS) after 144 weeks of treatment** (Expanded Access Program)

Park et al. AES 2023: Long-Term Effectiveness of CBD Against Focal-Onset Seizures in TRE (50%, 75% and 100% Response Rates)

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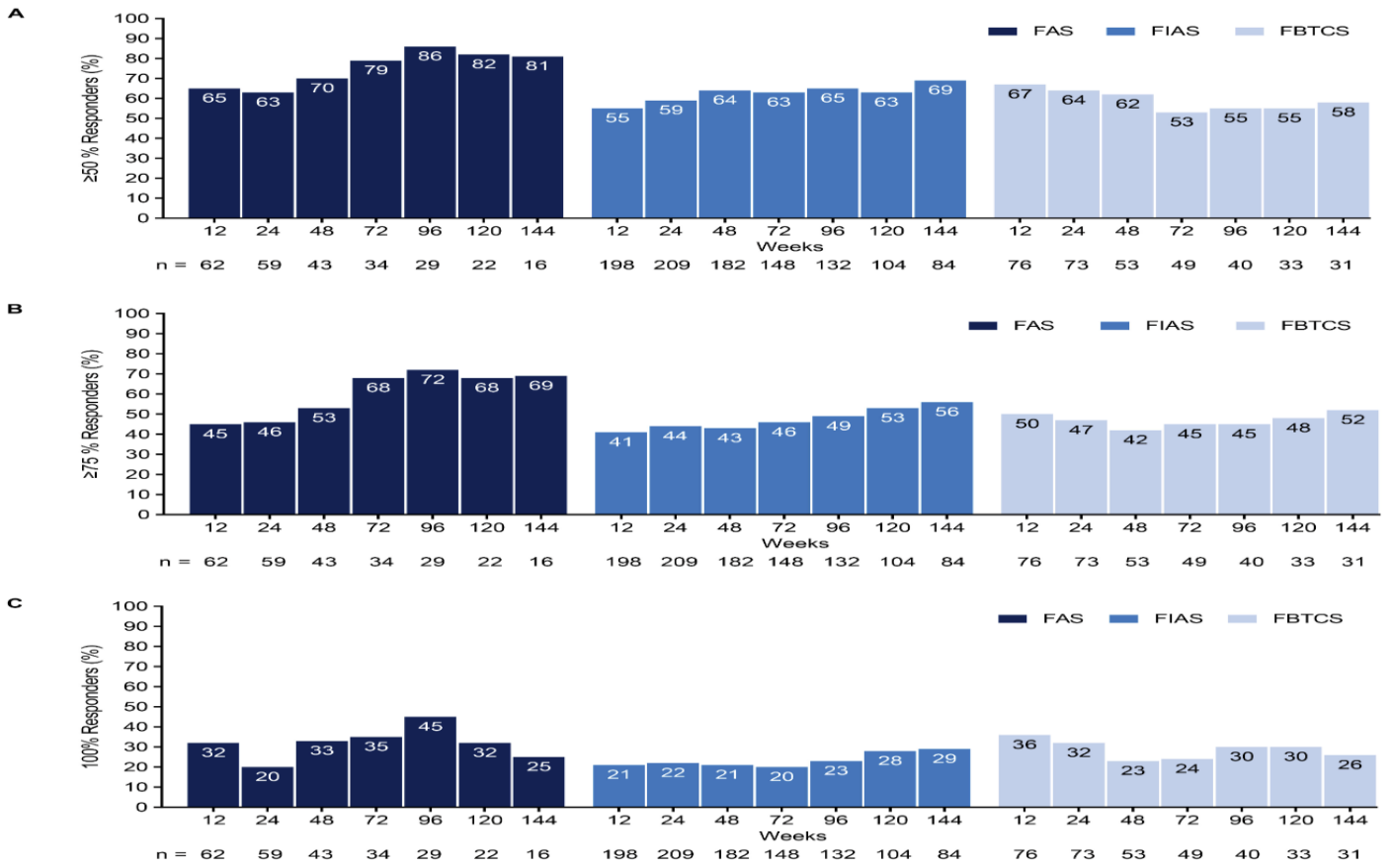
≥50% Responders

≥75% Responders

100% Responders

Figure 2. Treatment response rates: (A) ≥50% reduction, (B) ≥75% reduction, and (C) 100% reduction in FAS, FIAS, and FBTCS.



FAS, focal aware seizures; FIAS, focal impaired awareness seizures; FBTCS, focal to bilateral tonic-clonic seizures.

AES = American Epilepsy Society
TRE = Treatment-Resistant Epilepsies

Park et al. AAN 2024: Long-Term Effectiveness of CBD Against Focal-Onset Seizures in TRE (50%, 75% and 100% Response Rates)

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ABSTRACT (https://index.mirasmart.com/AAN2024/SearchResults.php?Author_Institution=&Program_Number=&Topic=&Session_Name=&Author=Park%2C+Yong&Title=)

- **Long-term Effectiveness of Cannabidiol (CBD) Against Focal-onset Seizures in Treatment-resistant Epilepsies (TRE): Experience from the Expanded Access Program (EAP)**
- **Objective:** To report the effect of CBD in EAP patients with focal-onset seizures, including focal aware seizures (FAS), focal impaired awareness seizures (FIAS), and focal to bilateral tonic-clonic seizures (FBTCS).
- **Background:** Four-year EAP results demonstrated that CBD was associated with sustained seizure improvement in TRE.
- **Design / Methods:** Patients received plant-derived highly purified CBD (Epidiolex®; 100 mg/mL oral solution) starting at 2–10 mg/kg/d and further titrated to a maximum of 25–50 mg/kg/d. Percentage change from baseline in median monthly frequency of focal seizures and responder rates (RRs) across 12-week intervals through 144 treatment weeks were evaluated.
- **Results:**
- Of **892 EAP patients**, 351 (39%) experienced focal seizures. Mean (range) age: 15.8 (<1–73.2) years.
- Median (range) Anti-Seizure Medications (ASMs) at baseline: 3 (0–10). Most common ASMs: clobazam (43%), levetiracetam (35%).
- Patients withdrew mainly because of lack of efficacy (18%) or AEs (5%).
- Median CBD exposure: 684 days (range, 10–1793) & Median top CBD dose: 25 mg/kg/d (IQR, 24–31).
- Baseline median (IQR) monthly seizure frequency: 28 (4–87) for FAS, 22 (7–76) for FIAS, and 12 (4–41) for FBTCS.
- CBD treatment was associated with median reduction of 67%–99% (FAS), 61%–78% (FIAS), and 50%–81% (FBTCS).
- The **FAS Response Rates (RRs)** were **61%–88% (≥50% reduction), 45%–72% (≥75% reduction), and 20%–46% (100% reduction).**
- The **FIAS RRs** were **55%–69%, 41%–56%, and 18%–29%, respectively.**
- The **FBTCS RRs** were **52%–69%, 41%–54%, and 23%–36%, respectively.**
- Among patients with any focal seizure, 90% reported AEs and 38% serious AEs; 7% withdrew due to AEs. Five deaths, not considered treatment-related, occurred in the cohort. Most common AEs: diarrhea (40%), convulsion (24%), somnolence (21%). Liver-related AEs (>1%) were increased ALT and AST (4% each) and abnormal liver function test (3%).
- **Conclusions: CBD treatment was associated with reduction in focal seizures with an acceptable safety profile.**

AAN 2024 Annual Meeting

PHYTANIX INTELLECTUAL PROPERTY (1)

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Phytanix patent families:

- **PTX0001 Patent Family**
  - "Terpenophenolic Compounds And Their Use"
  - Patent has been Granted
- **PTX0002 Patent Family**
  - "Terpenophenolic Scaffolds and a Method for Producing Same"
  - This patent builds on PTX001 family and covers more than 400 compounds

PHYTANIX INTELLECTUAL PROPERTY (2)
Patent Family Status

Patent Family Ref	Patent Owner	Country	Filing Date	Filing Code	Nat/Reg entry Date	Nat/Reg entry Number
PTX P0001 AUw	Phytotherapeutix Ltd*	Australia	31 March 2021	PCT/GB2021/050812	28 October 2022	2021248627
PTX P0001 BRw	Phytotherapeutix Ltd	Brazil	31 March 2021	PCT/GB2021/050812	28 September 2022	BR1120220196164
PTX P0001 CAw	Phytotherapeutix Ltd	Canada	31 March 2021	PCT/GB2021/050812	27 September 2022	3,177,186
PTX P0001 CNw	Phytotherapeutix Ltd	China	31 March 2021	PCT/GB2021/050812	28 November 2022	202180038597.7
PTX P0001 EPw	Phytotherapeutix Ltd	European Patent Office	31 March 2021	PCT/GB2021/050812	24 October 2022	21717177.6
PTX P0001 GBw	Phytotherapeutix Ltd	United Kingdom	31 March 2021	PCT/GB2021/050812	24 October 2022	2215746.5
PTX P0001 ILw	Phytotherapeutix Ltd	Israel	31 March 2021	PCT/GB2021/050812	28 September 2022	296861
PTX P0001 INw	Phytotherapeutix Ltd	India	31 March 2021	PCT/GB2021/050812	28 October 2022	202217061487
PTX P0001 JPw	Phytotherapeutix Ltd	Japan	31 March 2021	PCT/GB2021/050812	30 September 2022	2022-560311
PTX P0001 KRw	Phytotherapeutix Ltd	Republic of Korea	31 March 2021	PCT/GB2021/050812	28 October 2022	10-2022-7037909
PTX P0001 MXw	Phytotherapeutix Ltd	Mexico	31 March 2021	PCT/GB2021/050812	23 September 2022	MX/a/2022/011832
PTX P0001 USw	Phytotherapeutix Ltd	United States of America	30 September 2022	17/958,083	30 September 2022	17/958,083
PTX P0001 WO	Phytotherapeutix Ltd	WIPO	31 March 2021	PCT/GB2021/050812		
PTX P0001 ZAw	Phytotherapeutix Ltd	South Africa	31 March 2021	PCT/GB2021/050812	28 October 2022	2022/11785
PTX P0002 GB3	Phytotherapeutix Ltd	United Kingdom	30 January 2024	GB2401215.5		

*Phytotherapeutix Ltd is a UK subsidiary of Phytanix Inc.

FORMULATION TECHNOLOGY IN-LICENSED BY PHYTANIX :
Leucine improves the dissolution rate of a formulation of Ibuprofen

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PHYTANIX WILL UTILISE THIS TECHNOLOGY WITH THE AIM OF INCREASING THE ORAL BIOAVAILABILITY OF ITS DRUG DEVELOPMENT CANDIDATES

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Influence of coating material on the flowability and dissolution of dry-coated fine ibuprofen powders

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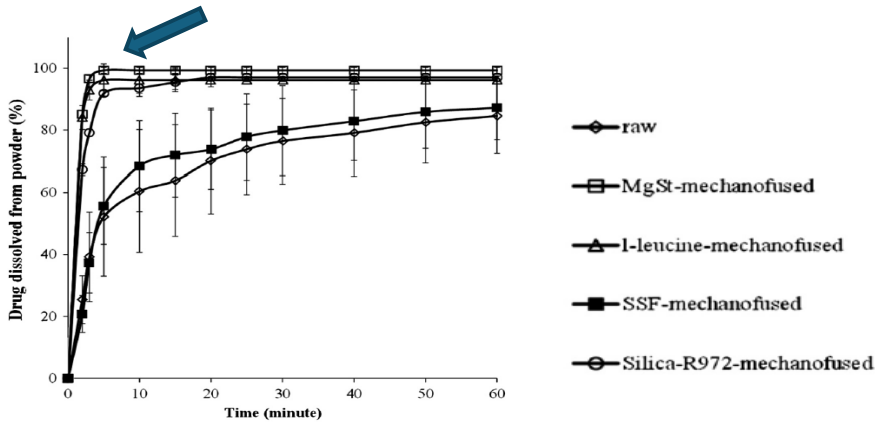

Fig. 5. Dissolution profile of the ibuprofen sample powders (error bars represent standard deviations, $n = 3$).

- Leucine improves the dissolution rate of a formulation of Ibuprofen
  - Dissolution rate is a marker of increased oral bioavailability
- Leucine increases the flowability of the powder (less sticky!)
  - Allows it to be spray dried more easily
- Leucine allows greater compactability of the powder
  - Can get more powder into a single capsule
- Leucine may improve the stability of the Active Pharmaceutical Ingredient (API) – to be confirmed
  - This will be particularly helpful for the unstable cannabinoid acids
- increases the flowability of the powder (less sticky!)

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ANY QUESTIONS ?

APPENDIX

July 29, 2024

Schedule 1 Status of Cannabis in the USA

- Cannabis is currently scheduled as Schedule 1 by the DEA under Federal Law (Controlled Substances Act 1970 & amendments)
- Under the law this means that it has “No medical value”
- Discussion as to whether the DEA will reschedule cannabis to Schedule 2 or Schedule 3 – yet to happen
- The 2018 “Farm Bill” exempted Hemp from this control as long as the THC content was below 0.3%w/w
- To date DEA has issued 8 such licences
- We have an opportunity to acquire one of these 8 licences

ASSET PURCHASE / IN-LICENSING AGREEMENTS IN PLACE

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- **Phytanix has a number of Licensing / Asset Purchase Agreements in place:**
- **Ferven Asset Purchase Agreement**
  - The terms of this agreement enables Ferven (and thus Alterola) to use a specific micro-organism for genetic engineering for the production of cannabinoids
- **Nano4M Licensing Agreement**
  - This covers the use of Nano4M nano formulation technology to be applied to Phytanix's Active Pharmaceutical Ingredients (APIs)
  - This technology has already been applied to Ibuprofen
  - It is anticipated that this may increase bioavailability between 4-5 fold

- **Phytanix is currently in discussions with a number of parties with regard to other acquisitions / mergers / in-licensing opportunities which includes:**
  - Extraction and Manufacturing capability
  - Other patented cannabinoid molecules with improved bioavailability
  - DEA Schedule 1 Licence