Finding the Medicine in Marijuana: new developments in cannabinoid medications

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GW Pharmaceuticals

CLRS

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GW Pharmaceuticals

- Founded in 1998 by Dr Geoffrey Guy and Dr Brian Whittle;
  - Specialists in development of plant-based pharmaceuticals, controlled substances and drug delivery systems;
  - Receives the full backing of Government peers and politicians.

- Controlled drug licences from the UK Home Office and MHRA govern all research activities
  - Permits cultivation of herbal starting materials;
  - Enables scientific studies concerning medicinal uses of various cannabis extracts;
  - Export licenses permit distribution of compounds to global partners.

Primary Aim:

Separation of prescription medicine from drug of abuse

Why did GW Choose to Develop a Cannabis-Derived Prescription Medication?

- The UK Government was seeking to separate patients from the stigma and controversy surrounding cannabis.
  - MS patients using cannabis were being arrested but then released by the courts, which brought the law into disrepute;
  - Government wanted to determine whether a medication could be developed in accordance with modern scientific standards.
  - Report by the Science and Technology Committee of UK House of Lords 1998.
- New research in the early 1990s demonstrated the existence and structure of the endocannabinoid receptor system (ECS).
  - Established the mechanism of action and the means to explore it;
  - Scientific interest in the area increased exponentially.
- Modern technology made it possible to study, formulate, and administer these compounds and also to standardize plant-derived products.

Developing Botanical Medications

GW's Manufacturing Process

Cuttings from clones ensures uniform material

Bespoke growth medium without fertilizers/pesticides

Tightly controlled irrigation, light & temp (12 weeks)

Botanical Raw Material **(BRM)**

GAP

Good agricultural process

Harvested, dried, milled & controlled storage

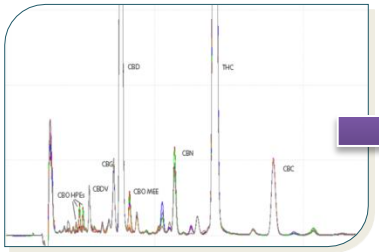
Primary extraction under controlled conditions

Further processing of primary extract

Botanical Drug Substance **(BDS)**

GMP

Good manufacturing process



Highly characterised QC & release BDS

Formulation of finalised bulk solution

Filter & fill bulk solution, QC and release

Botanical Drug Product **(BDP)**

Sativex is a Precise Mixture of 2 BDSs

THC Clones

CBD Clones

Botanical Raw Material (BRM)

THC BRM

CBD BRM

Botanical Drug Substance (BDS)

THC BDS

THC = 67.0 %
CBD = 0.3 %

CBD BDS

THC = 2.6 %
CBD = 65.9 %

Sativex

Botanical Drug Product (BDP)

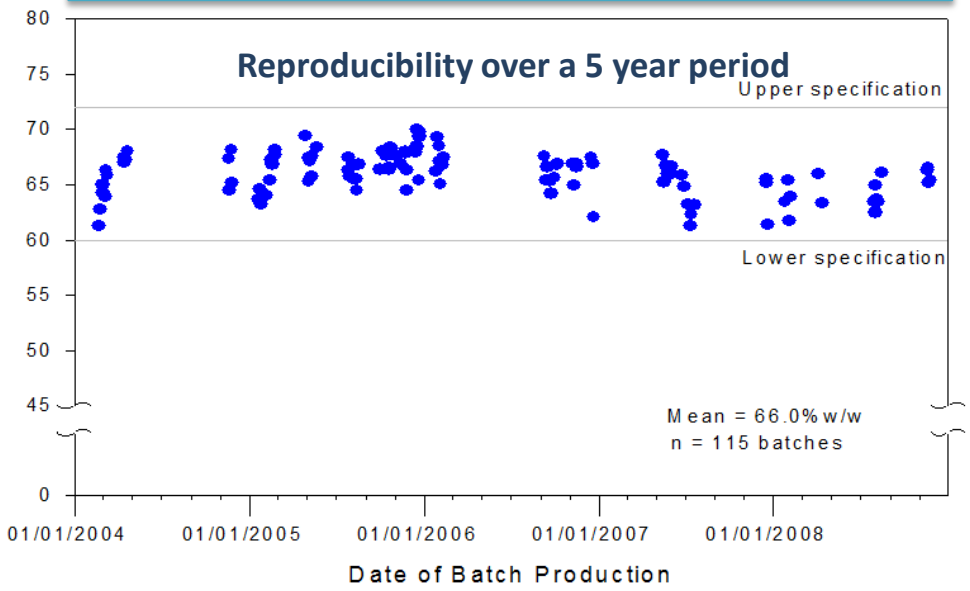
Final product = precise 1:1 ratio of THC to CBD

Growing on a Commercial Scale

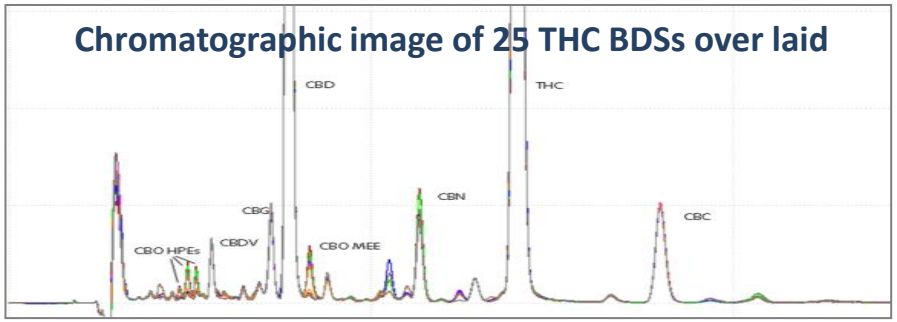
Production of a Cannabinoid Medicine:
Meeting Strict Pharmaceutical Manufacturing Standards

- Strict control for both the growing conditions (highly regulated facility) and starting materials (plant clones)
- Proprietary technology produce extracts and pure compounds
- Fully characterise constituents of the extract to the same rigorous standard as other pharmaceuticals (11 CBs)
- Quality control tests at all steps in the manufacturing process
- Conformance to detailed specification agreed by FDA: “fingerprint”

CBD Content Between Batches



Extract Characterisation



What is Sativex®?

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There's more to cannabis than THC!

- Cannabis plant is the unique source of cannabinoids
- Cannabis used centuries ago possessed a 1:1 CBD:THC ratio

THC
(tetrahydrocannabinol)

- is analgesic, anti-spasmodic, anti-tremor, anti-inflammatory, appetite stimulant, anti-emetic

CBD
(cannabidiol)

- is anti-inflammatory, analgesic, anti-convulsant, anti-psychotic, anti-oxidant, neuroprotective;
  - does not bind to cannabinoid receptors
  - does bind to other receptors in the body
  - reduces the negative effects of THC
  - has been bred out of modern herbal cannabis!

Components cont.

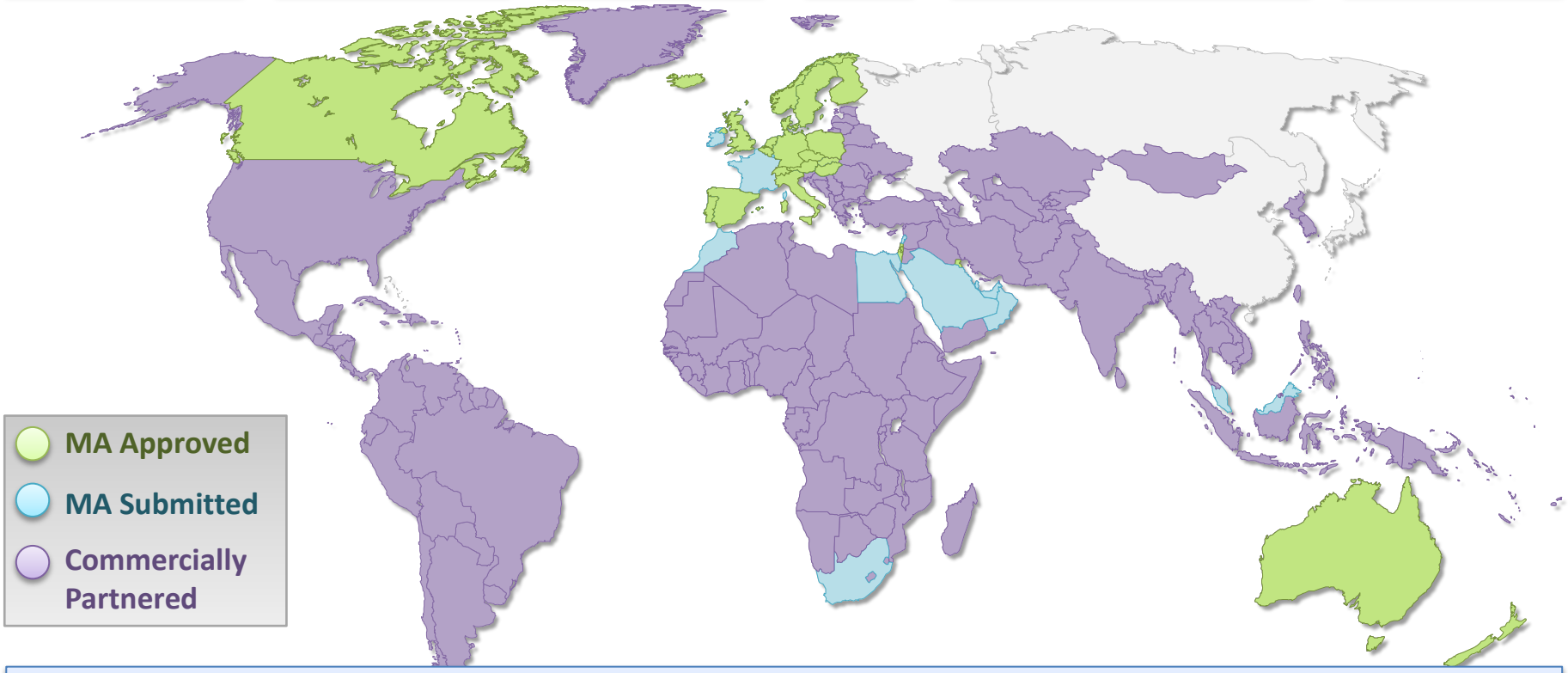
- 60-100 cannabinoids in total, each with their own--often complementary—pharmacology, e.g., CBDV, THCV, CBG, CBN, CBC, etc., for different medical conditions
  - Only THC is psychoactive
  - Multiple extracts can be blended to form new products
- There are also other non-cannabinoid active components, e.g., terpenes, flavonoids
- Real issue is that plant extracts must be adequately characterized and standardized

Sativex® (USAN: nabiximols)

- Each ml contains:
  - THC and CBD as well as specific minor cannabinoids and other non-cannabinoid components
- Excipients:
  - Ethanol anhydrous
  - Propylene glycol
  - Peppermint oil (0.05%)
- Pharmaceutical form:
  - Oromucosal solution in spray container
- Each 100 microlitre spray contains:
  - 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD)

Sativex®:Approved in 24 Countries for MS Spasticity

Bayer	Almirall	Otsuka	NEOPHARM	NOVARTIS	IPSEN
UK and Canada	EU and Mexico	United States	Israel	Africa, Middle East, Asia	Latin America



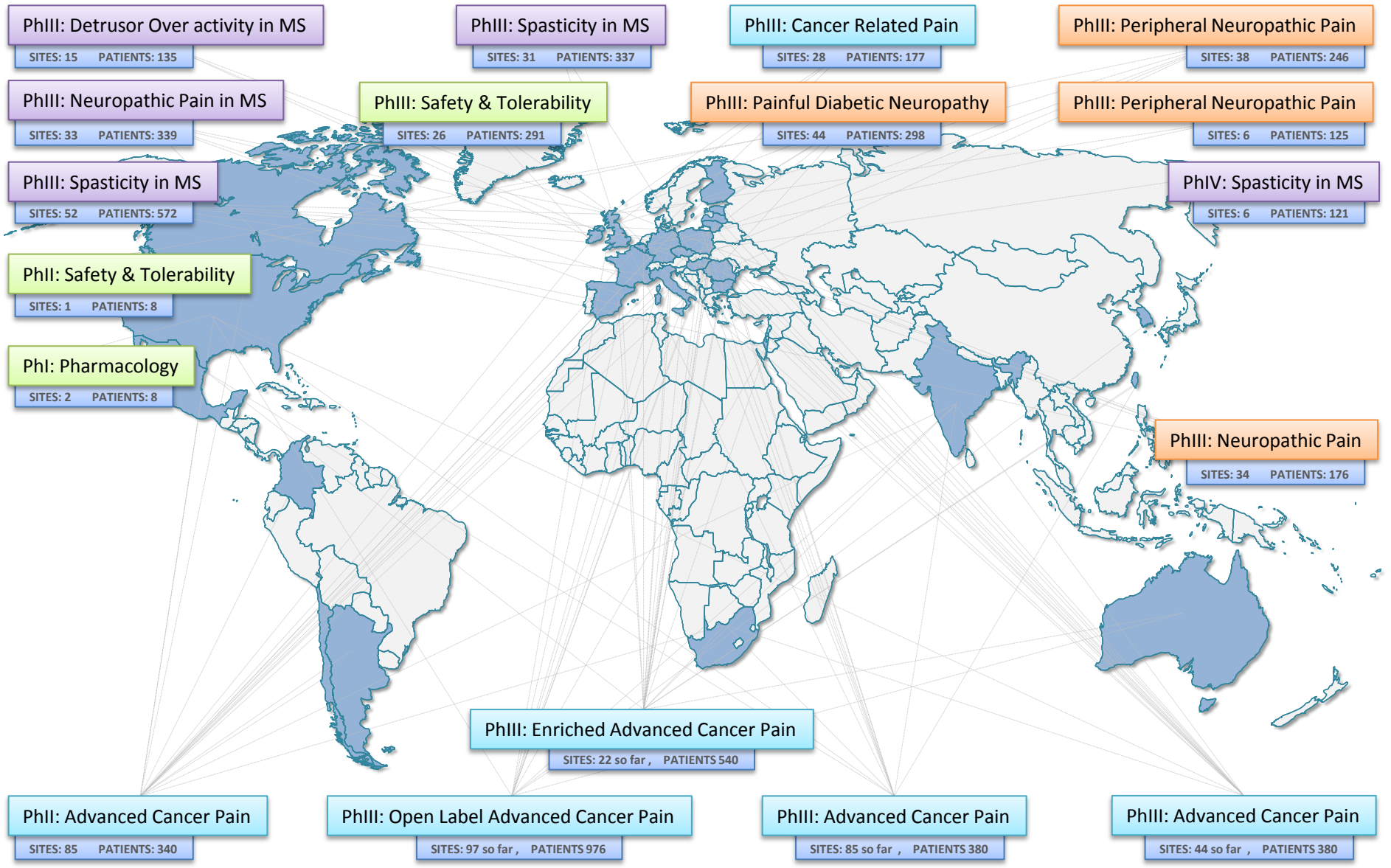
Current Phase 3 Programme: Advanced Cancer Pain

Indication: *Add-on treatment of persistent pain in people with advanced cancer who experience inadequate pain relief from optimized chronic opioid therapy*

Substantial body of positive Phase 2 data (over 530 patients) – 3 Phase 3 trials ongoing plus long term extension

Sativex Clinical Trials: 2000 – 2013

3244 Patients in 484 Sites (excluding extension trials) so far

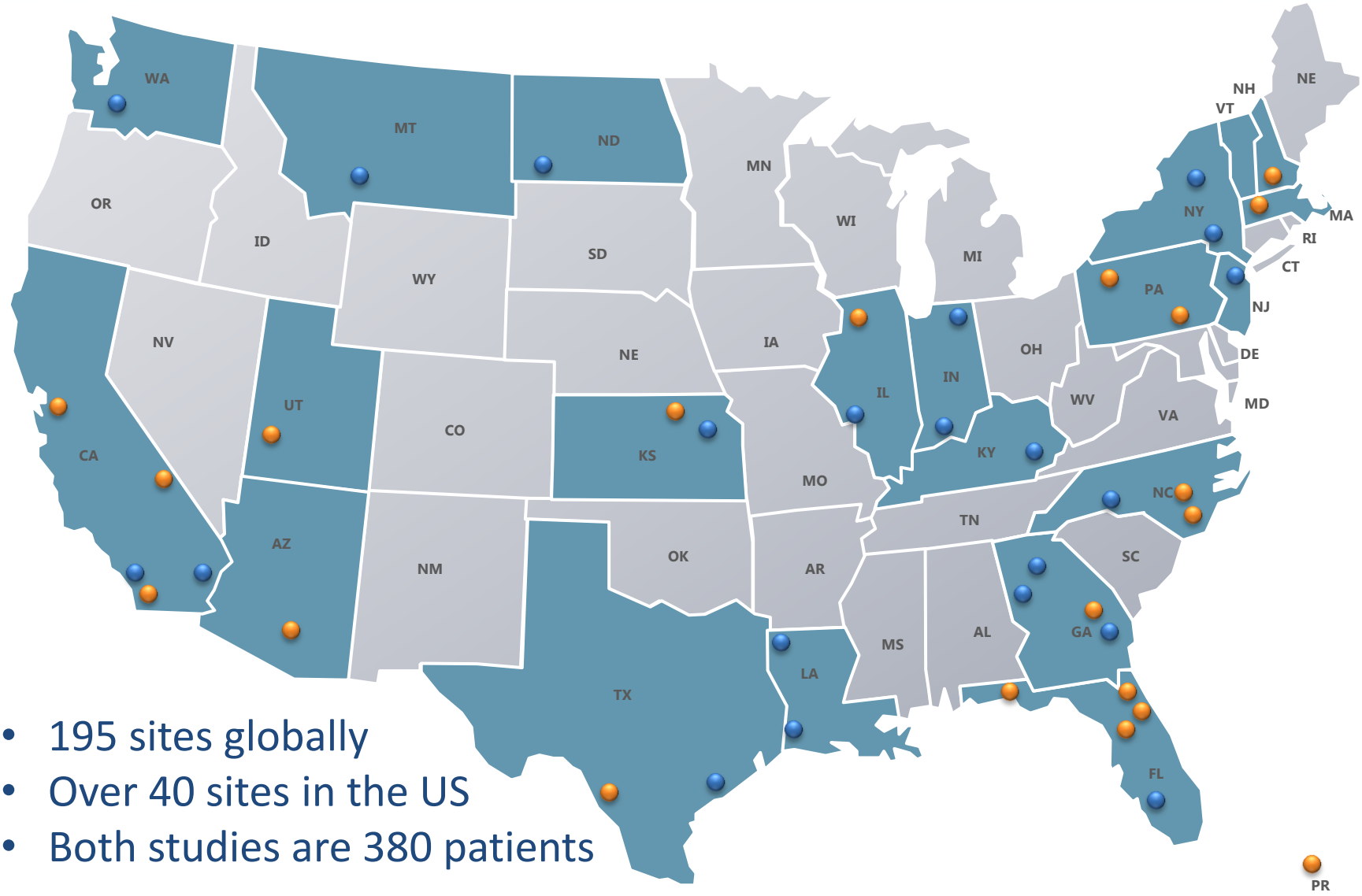


Sativex® in the United States

Initial Target: Cancer Pain

- Indication: Advanced cancer patients with pain not wholly alleviated with current optimized opioid treatment
  - Treats persistent, not breakthrough, pain
  - Added on to existing opioid regimen
  - US Sativex cancer pain use patent granted (expiry Sept 2026)
- Substantial body of positive Phase II data including over 500 patients
  - GW/Otsuka FDA “end of Phase II” discussions held
- 3 Phase III trials ongoing plus long term extension
  - First two Phase III trials well underway (n=380 in each study) intended for FDA submission and other global regulatory authorities
  - Third Phase III trial recently commenced
    - Different “enriched” study design. Part A n=540, Part B n=216

Sativex Sites – Phase III Cancer Pain Trials



- 195 sites globally
- Over 40 sites in the US
- Both studies are 380 patients

Sativex® is not "medical marijuana"!

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“Medical marijuana” does not comport with the modern medical paradigm

- Composition (% of THC) of herbal cannabis varies significantly
  - depends on strains, cultivation and storage, etc.
  - “laboratories” often cannot replicate results
- Modern cannabis bred to exhibit (only) high levels of THC
  - no meaningful levels of other cannabinoids such as CBD
- Delivery systems (smoked/vaporized, baked goods, teas) do not provide a standardized dose;
  - no precedent for administering any crude herbal material in a manner that reliably achieves a reproducible dose and produces no carcinogens
- Contamination with microbes, heavy metal, and pesticides a real possibility.

Modern paradigm cont.

- Distribution does not take place within regulated supply chain for pharmaceuticals
  - “collectives” and “cooperatives”

- No collection of adverse event or efficacy data
  - impossible to know who is really benefiting or being harmed
- Medical advice being given by untrained and unlicensed individuals
  - broad efficacy claims
  - often no meaningful physician supervision
  - no labelling with risk information or instructions for use
- Patients cannot obtain health insurance coverage

Vaporization: safety issues

- Vaporization does not remove all toxic byproducts and resolve safety issues:
- Vaporizers vary significantly in quality and features, none FDA approved;
- If temperature can be set up to 200-230°C, toxic combustion products **will** be produced;
- Even at lower temperatures, some tars produced, and delivery of cannabinoids becomes very inefficient;
- Uncertain whether all microbes destroyed;
- Content of vapor determined by underlying quality/contamination of herbal material;
- More ammonia may be inhaled because no loss in side stream smoke.

The Disadvantages of Giving Herbal Cannabis a "free pass"

- By creating an exception for cannabis, we are preventing the development of quality, safety and efficacy data that would allow it to become broadly accepted as a true medication

- The vast majority of patients want a product that is standardized by composition and dose and about which their physicians can offer meaningful advice

“Medical Marijuana” Manufacturing Process

Sativex® GMP Manufacturing Process

Uniform plants grown in controlled conditions

Highly controlled drying conditions

Highly controlled Extraction process

Fully automated GMP manufacturing

Fully automated GMP labelling & packing

GMP packaging, includes product information, tamper evidence and anti-counterfeit features

Sativex®

Abuse Potential/safety issues

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Cannabinoid Therapeutic Window

Objective:

- To provide and maintain therapeutic blood and tissue levels of key cannabinoid components without incurring unacceptable side effects

Challenges:

- Inter-subject pharmacokinetic variability
- Minimise Side Effects (psychoactivity) caused by rapid rate of rise of plasma levels in inhaled route
- Limitations of oral route
- Poor aqueous solubility

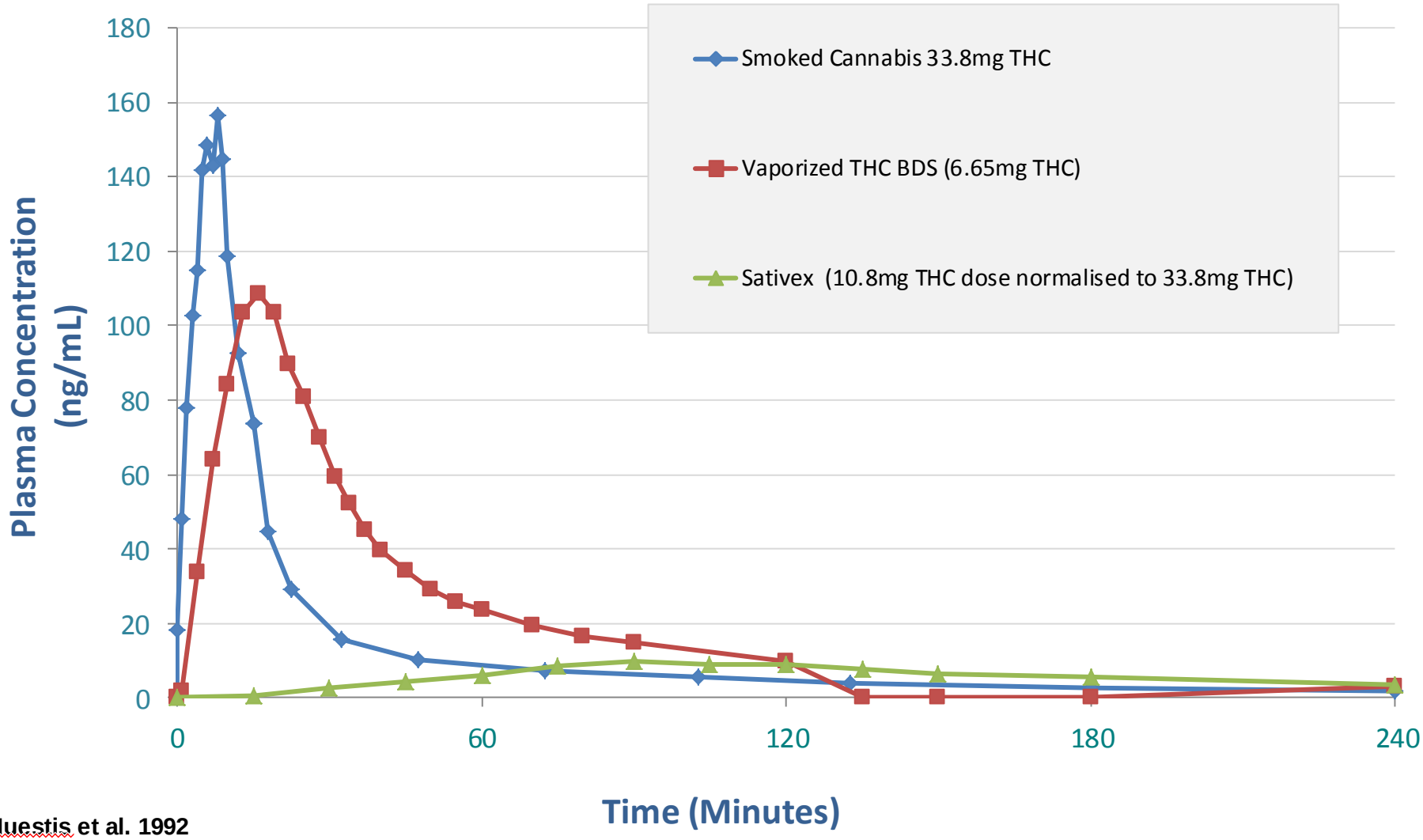
Predictable maintenance of acceptable risk / benefit

Therapeutic Window - Solutions

- Cannabinoid ratios widen window
  - CBD may counter some of the side effects
  - CBD appears to delay and reduce intensity of intoxication
- Route and method of delivery (DDS)
  - Mucosal route far less variable than Oral (GI)
  - Mucosal absorption decreases first pass metabolism
- Rate of absorption controlled
- Formulation and dosage form
  - Oromucosal spray
- Self-titration
  - Predictability

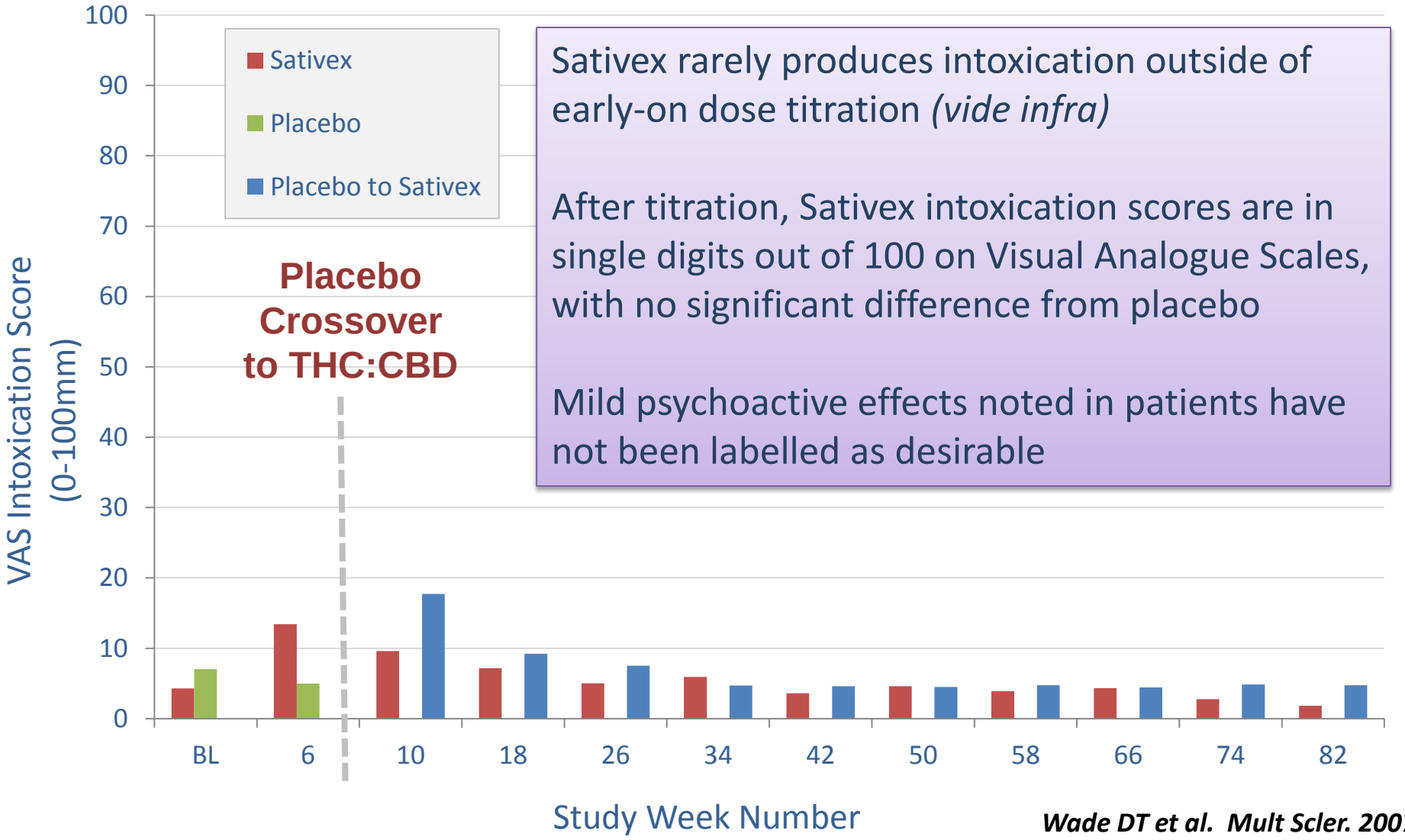
Predictable maintenance within therapeutic window

Plasma Concentration Time Curves



Huestis et al. 1992

Intoxication



Sativex rarely produces intoxication outside of early-on dose titration *(vide infra)*

After titration, Sativex intoxication scores are in single digits out of 100 on Visual Analogue Scales, with no significant difference from placebo

Mild psychoactive effects noted in patients have not been labelled as desirable

Wade DT et al. Mult Scler. 2007

Abuse Liability: Comparison with Marinol

Title	A Randomized, Double-blind, Placebo-controlled, Cross-over Study to Evaluate the Abuse Potential of Sativex® in Subjects With a History of Recreational Marijuana Use
Inclusion	Healthy, regular marijuana users who show the capacity to 'recognise' the effects of Marinol during a qualification period (n=30 randomised, n=23 completers)
Dose	Sativex 4 sprays, 8 sprays and 16 sprays (all taken at once) Marinol 20mg and 40mg
Primary endpoints	Drug Liking: Subjective Drug Value: ARCI morphine-benzedrine sub-scale (Maximum effect as primary analysis)
Secondary endpoints	Various VAS scales for positive and negative effects (VAS anchors: 0-100) Assessments of cognition

Abuse Liability cont.

- At low doses (4 sprays, containing 10.8mg THC), the abuse potential Sativex® is not statistically significantly different to that of placebo for the primary endpoints (and most secondary endpoints)

- At mid and high doses (8 & 16 sprays, containing 21.6 & 43.2mg THC), the abuse potential Sativex® is not statistically significantly different to that of Marinol (20mg and 40mg respectively) for the primary endpoint

Cognitive Assessments

- Short-term cognitive impairment predicts long-term cognitive impairment
- Cognitive impairment may predict functional outcomes
  - i.e. retaining good cognitive performance is good for function
- Many medications may cause cognitive impairment

Three Tests Performed:

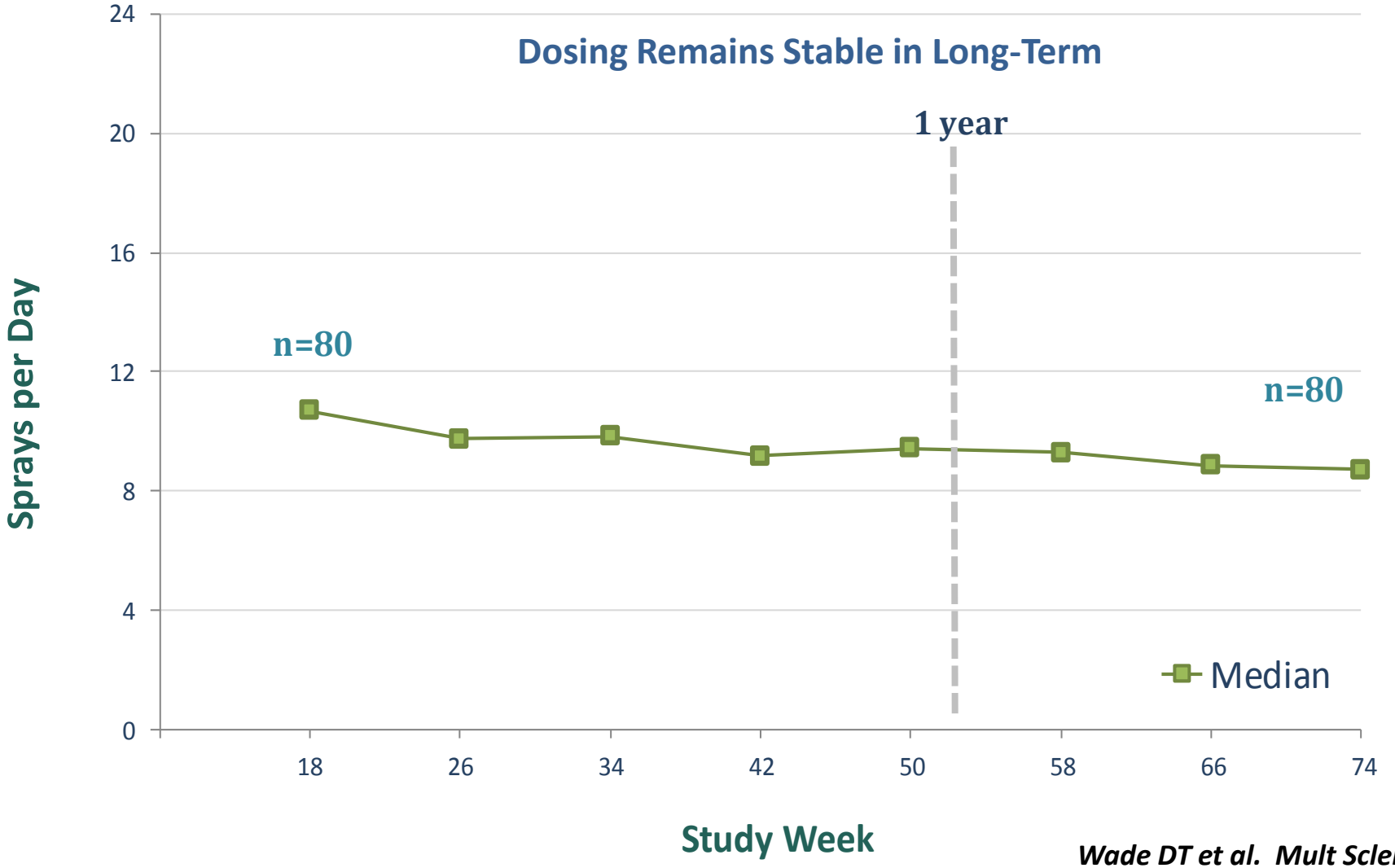
1. Sternberg Test (Short-Term Memory)
   - No significant effect of Sativex at any dose level
   - Marinol significantly different from placebo at 40 mg dose (p=0.01)
2. Divided Attention (Simultaneous performance of different tasks)
   - No negative impact of Sativex on divided attention
   - High dose Marinol significantly greater times logged than placebo
3. Choice Reaction Time (Measures accuracy of responses)
   - No significant effect of Sativex or Marinol on any of the parameters assessed

Unlike Marinol, at single doses of 4 sprays, 8 sprays and 16 sprays, Sativex does not produce short-term cognitive impairment

No Tolerance or Dose Escalation

- Tolerance a common problem with use of opioids
- In over 1500 patient-years of experience, no dose escalation or tolerance has been observed
  - Long term extension studies in MS and peripheral neuropathic pain show stable/decreased doses after months/years of administration
  - Patient registry data confirms
- Sudden withdrawal of medication in MS patients taking it for over one year produced a gradual re-emergence of symptoms in 7-10 days, but no withdrawal syndrome or side effects requiring treatment.
- No signals of abuse or diversion in 8 yrs of prescription use

Tolerance – Sativex Sprays Per Day



Wade DT et al. Mult Scler. 2007

Future Cannabinoid Medications

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International Academic Network

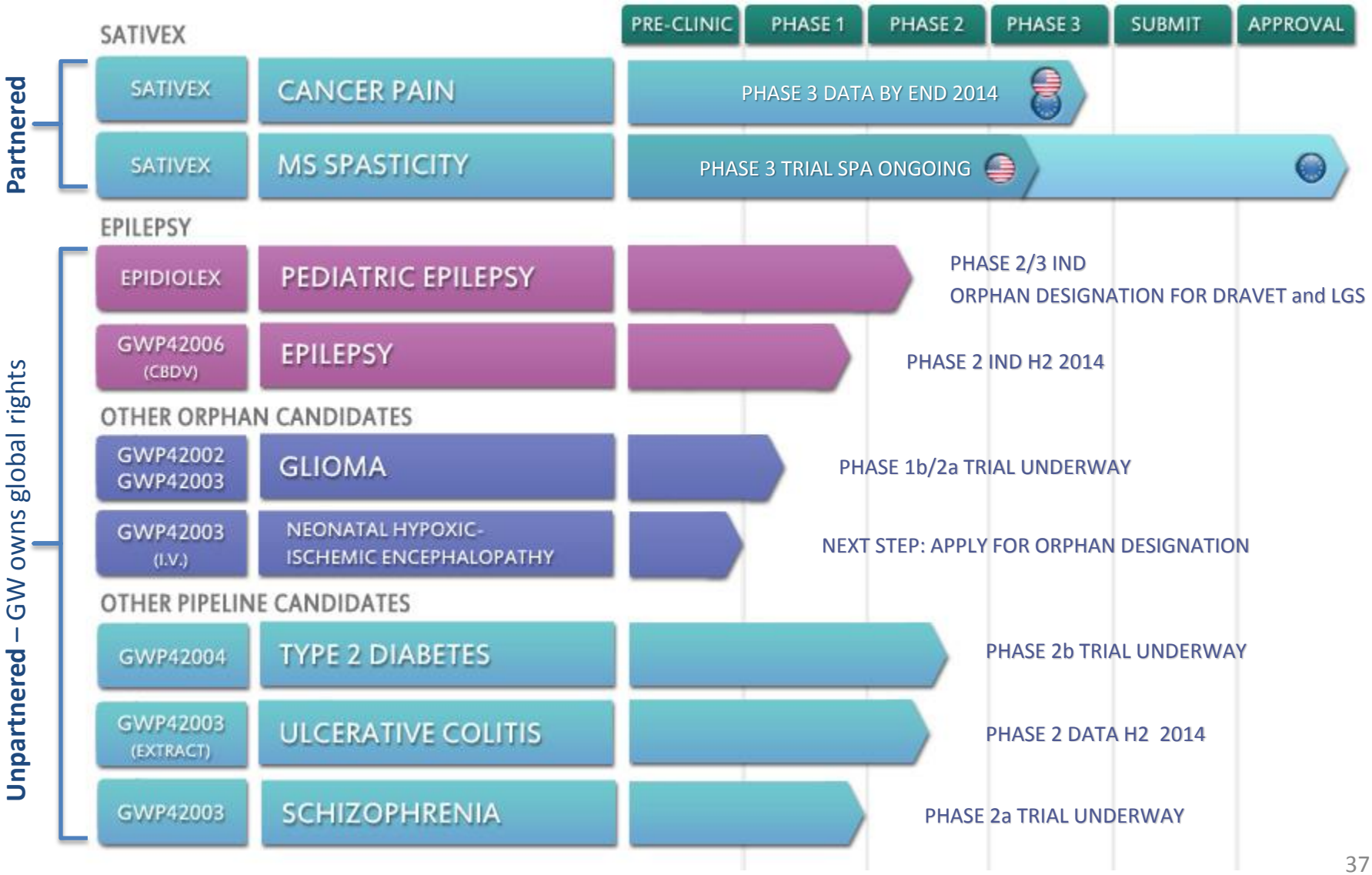
- Prof Roger Pertwee
- Prof Vincenzo Di Marzo
- Prof Raphael Mechoulam
- Prof Mike Cawthorne
- Prof Jimmy Bell
- Prof Clive Page
- Prof Tamas Biro
- Prof Dave Kendall
- Prof Yasmin Hurd
- Prof Daniela Parolaro
- Prof Ruth Ross
- Prof Mauro Maccarone
- Pro Fernadez-Ruiz
- Dr Ben Whalley
- Dr Marilyn Huestis
- Dr Manuel Guzman
- Dr Guillermo Velasco
- Dr Cristina Sanchez
- Dr Pepe Martinez-Orgado
- Dr Angelo Izzo
- Dr Alistair Nunn
- Dr Saoirse O'Sullivan
- Dr Sabatino Maione
- Dr Barbara Costa

Etc….

Worldwide Cannabinoid Research

An Expansive Pipeline

Therapeutic Areas Defined by Nature of Cannabinoids



Conclusions

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What Do Modern Cannabis-Derived or Cannabinoid Products Get Us?

- Process governed by science
- Patients will have legitimate prescriptions and health care insurance coverage
- Products distributed and dispensed through monitored drug supply channels
- Data from controlled clinical studies available to physicians
- Products standardized by composition and dose
- Medication administered in appropriate dosage form
- Manufacturers accountable for quality

THANK YOU

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