RespireRx Pharmaceuticals Inc

OTC QB: RSPI

# Drug Re-purposing: A Case Study of Dronabinol

September 7, 2022

# Forward Looking Statements

RespireRx Pharmaceuticals Inc

**FORWARD LOOKING STATEMENTS**

*This presentation contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act") and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and the Company intends that such forward-looking statements be subject to the safe harbor created thereby. These might include statements regarding the Company's future plans, targets, estimates, assumptions, financial position, business strategy and other plans and objectives for future operations, and assumptions and predictions about research and development efforts, including, but not limited to, preclinical and clinical research design, execution, timing, costs and results, future product demand, supply, manufacturing, costs, marketing and pricing factors.*

*In some cases, forward-looking statements may be identified by words including "assumes," "could," "ongoing," "potential," "predicts," "projects," "should," "will," "would," "anticipates," "believes," "intends," "estimates," "expects," "plans," "contemplates," "targets," "continues," "budgets," "may," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words, and such statements may include, but are not limited to, statements regarding (i) future research plans, expenditures and results, (ii) potential collaborative arrangements, (iii) the potential utility of the Company's products candidates, (iv) reorganization plans, and (v) the need for, and availability of, additional financing. Forward-looking statements are based on information available at the time the statements are made and involve known and unknown risks, uncertainties and other factors that may cause our results, levels of activity, performance or achievements to be materially different from the information expressed or implied by the forward-looking statements in this presentation.*

*These factors include but are not limited to, regulatory policies or changes thereto, available cash, research and development results, issuance of patents, competition from other similar businesses, interest of third parties in collaborations with us, and market and general economic factors, and other risk factors disclosed in "Item 1A. Risk Factors" in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2021, as filed with the SEC on April 15, 2022 (the "2021 Form 10-K") and any other relevant SEC filings.*

*You should read these risk factors and the other cautionary statements made in the Company's filings as being applicable to all related forward-looking statements wherever they appear in this presentation. We cannot assure you that the forward-looking statements in this presentation will prove to be accurate and therefore prospective investors, as well as potential collaborators and other potential stakeholders are encouraged not to place undue reliance on forward-looking statements. You should read this presentation completely. Other than as required by law, we undertake no obligation to update or revise these forward-looking statements, even though our situation may change in the future.*

*We caution investors, as well as potential collaborators and other potential stakeholders not to place undue reliance on any forward-looking statement that speaks only as of the date made and to recognize that forward-looking statements are predictions of future results, which may not occur as anticipated. Actual results could differ materially from those anticipated in the forward-looking statements and from historical results, due to the risks and uncertainties described in the 2020 Form 10-K and in this presentation, as well as others that we may consider immaterial or do not anticipate at this time. These forward-looking statements are based on assumptions regarding the Company's business and technology, which involve judgments with respect to, among other things, future scientific, economic, regulatory and competitive conditions, collaborations with third parties, and future business decisions, all of which are difficult or impossible to predict accurately and many of which are beyond the Company's control. Although we believe that the expectations reflected in our forward-looking statements are reasonable, we do not know whether our expectations will prove correct. Our expectations reflected in our forward-looking statements can be affected by inaccurate assumptions that we might make or by known or unknown risks and uncertainties, including those described in the 2021 Form 10-K and in this presentation. These risks and uncertainties are not exclusive and further information concerning us and our business, including factors that potentially could materially affect our financial results or condition, may emerge from time to time.*

*For more information about the risks and uncertainties the Company faces, "Item 1A. Risk Factors" in our 2021 Form 10-K. Forward-looking statements speak only as of the date they are made. The Company does not undertake and specifically declines any obligation to update any forward-looking statements or to publicly announce the results of any revisions to any statements to reflect new information or future events or developments. We advise investors, as well as potential collaborators and other potential stakeholders to consult any further disclosures we may make on* related subjects in our annual reports on Form 10-K and other reports that we file with or furnish to the SEC.

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# RespireRx - Product Development Status

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| | Preclinical | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|
| *ResolutionRx - Cannabinoids* | | | | |
| Dronabinol – OSA | → | → | → | |
| | | | | |
| *EndeavourRx - Neuromodulators* | | | | |
| **AMPAkines** | | | | |
| CX717 - ADHD | → | → | → | |
| CX1739 - Spinal Cord Injury | → | → | → | |
| CX1942 –follow-up compound | → | | | |
| **GABAkines** | | | | |
| KRM-II-81 – Epilepsy/Pain | → | | | |

# *Attractiveness of Re-Purposing of Dronabinol*

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***1. Development of Pharmaceutical Cannabinoids*** - refers to the development of cannabinoids according to FDA and other foreign accepted regulatory pathways by which a company receives approval to market and sell a new drug.

***2. Defined Regulatory Route to Commercialization*** - 505(b)(2) NDA in US creates expedited path to market by allowing publicly available safety data.

***3. Intellectual Property*** – issued and pending patents claiming cannabinoid compositions and methods for treating cannabinoid-sensitive disorders, including sleep apnea and other conditions.

***4. Very Large Market*** - a sleep-related breathing disorder that afflicts an estimated 60 million people in the US, Germany and UK combined.

***5. Clinical Validation*** - Phase 2A clinical trial completed demonstrating the ability of dronabinol to significantly reduce the symptoms of obstructive sleep apnea (“OSA”)

# Dronabinol Reduces Apnea in OSA Patients

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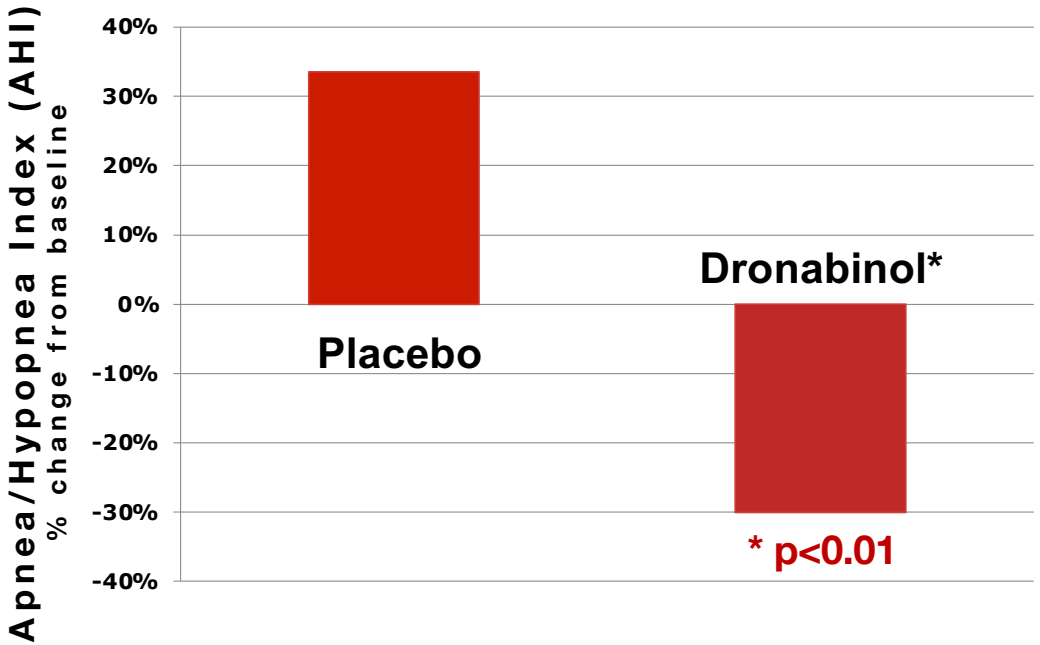
## Phase 2A Proof of Concept Trial of Dronabinol in OSA




- 3-Week Dose-ascending Study n =17
- Statistical Analysis Across All Doses & Times

[1] Published in Frontiers in Psychiatry January 2013 | Volume 4 | Article 1

# Obstructive Sleep Apnea is a National Epidemic

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| Disease State | Estimated US Prevalence | Annual Estimated Cost to Society | Annual Indicated Drug Therapy Expenditures |
|---|---|---|---|
| OSA[1-5] | 29.4 MM | $162.0 Billion | $ 0 |
| Asthma[6,7] | 16.4 MM | $18.3 Billion | $13.5 Billion |
| Hypertension[8-10] | 43.2 MM | $73.4 Billion | $48.5 Billion |
| Diabetes[11,12] | 23.5 MM | $174 Billion | $20.6 Billion |

1 Obstructive sleep apnea and sleep. National Sleep Foundation Web site.
2 Manufacturer Recommendations
3 Qualitative Market Research, Physician / Patient interviews, 2010
4 CPAP Supply USA,
5 American Sleep Apnea Association, 2010
6 Asthma & Allergy Foundation of America
7 Espicom Business Intelligence's New Drug Futures, 2006
8 Burt, V., et al., Hypertension, 2005
19 Lloyd-Jones, D., et al., Circulation 119(3):e21-181, 2009
10 Acmite Market Intelligence, 2008
11 Arrowhead, Gloabal Diabetes Market, 2006
12 American Diabetes Assoc., 2007

# Difficulties Unique to Dronabinol

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***1. Banks*** - Confused pharmaceutical cannabinoids with plant cannabis growing and sales

***2. Fund Raising*** – Cannabis investors focused on sales of plant based cannabis and traditional investors confused pharmaceutical cannabinoids with cannabis.

- Raised approximately $10 million equity, debt and NIH grants

***3. Intellectual Property*** – issued patents with limited life claiming cannabinoid compositions and methods for treating cannabinoid-sensitive disorders, including sleep apnea.

- Additional patents pending claiming use, dosage, blood levels, controlled release patterns with priority to November 2010 and patents pending claiming composition of matter and method of treatment for new formulations of cannabinoids, extending until 2041,

***4. API*** – traditional manufacturers not experienced with handling Schedule 1 API

- Joint development agreement in which Purisys will provide in-kind funding for all API supplies prior to NDA approval in exchange for an exclusive purchase agreement and limited participation in the success of the product

# THE PACE Clinical Trial: Pharmacotherapy of Apnea by Cannabimimetic Enhancement – A Phase 2B Study

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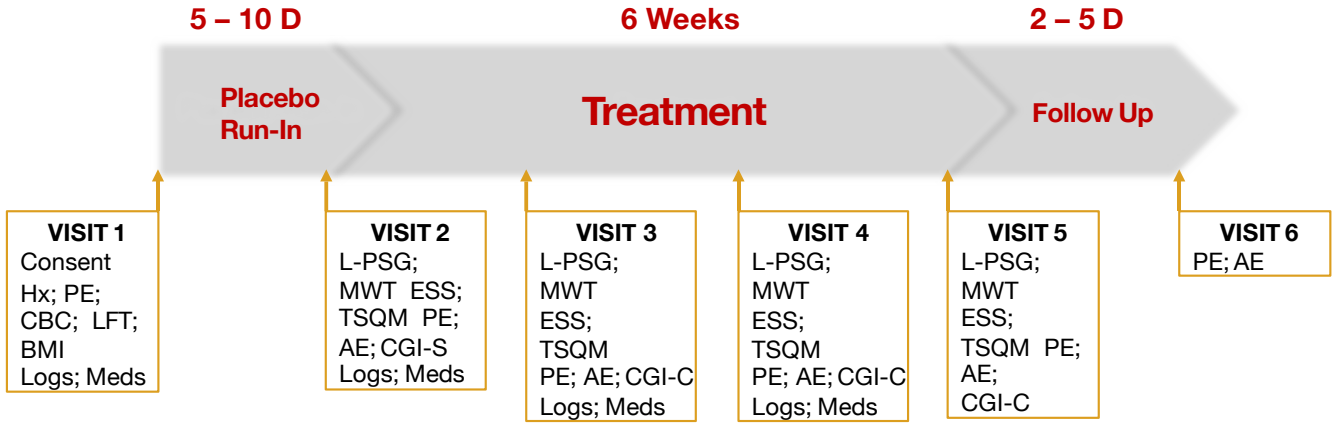
- Randomized, Placebo-controlled, Parallel Groups, Multi-site Trial in Patients with Moderate to Severe OSA, n=73
- Study Drug: Dronabinol (Overencapsulated Marinol®): 2.5 mg or 10 mg QD
- Dose Administration: 60 minutes before bedtime
- Inclusion: Age 21 – 64;  AHI 15 – 50; Epworth Sleepiness Scale (ESS) ≥ 7; Body Mass Index (BMI) ≤ 45
- Exclusion: Shift Work or OSA Tx within 1 mo; Medical Co-morbidity; Psych Dx; CNS  Active Meds




PACE Enhancement Cannabimimetic Apnea by Pharmacotherapy of Clinical Trial

# The Phase 2B PACE Trial in OSA: Final Overall Results

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## Statistically significant improvement in Primary Outcome Measures

- Apnea-Hypopnea Index (AHI) (2.5 and 10 mg)
- ESS Sleepiness Scale (10 mg)
- Overall Patient Satisfaction (10 mg)

# Results of 6-Week Treatment: Dronabinol Reduces AHI

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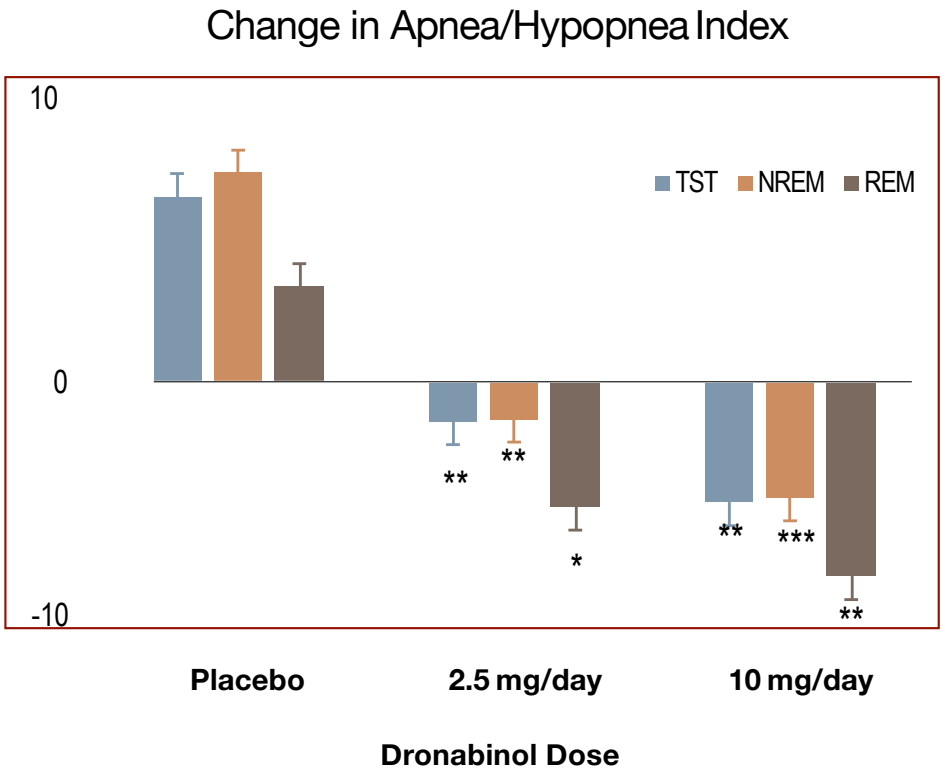
## Positive Effects of Dronabinol vs. Placebo in TOTAL, REM & NREM Sleep Demonstrate Efficacy




Compared to placebo

* p<.05
** p≤.02
*** p≤.005

PACE Enhancement Cannabimimetic Apnea by Pharmacotherapy of Clinical Trial

# The Pace Trial Replicates the Phase 2A Study[1]

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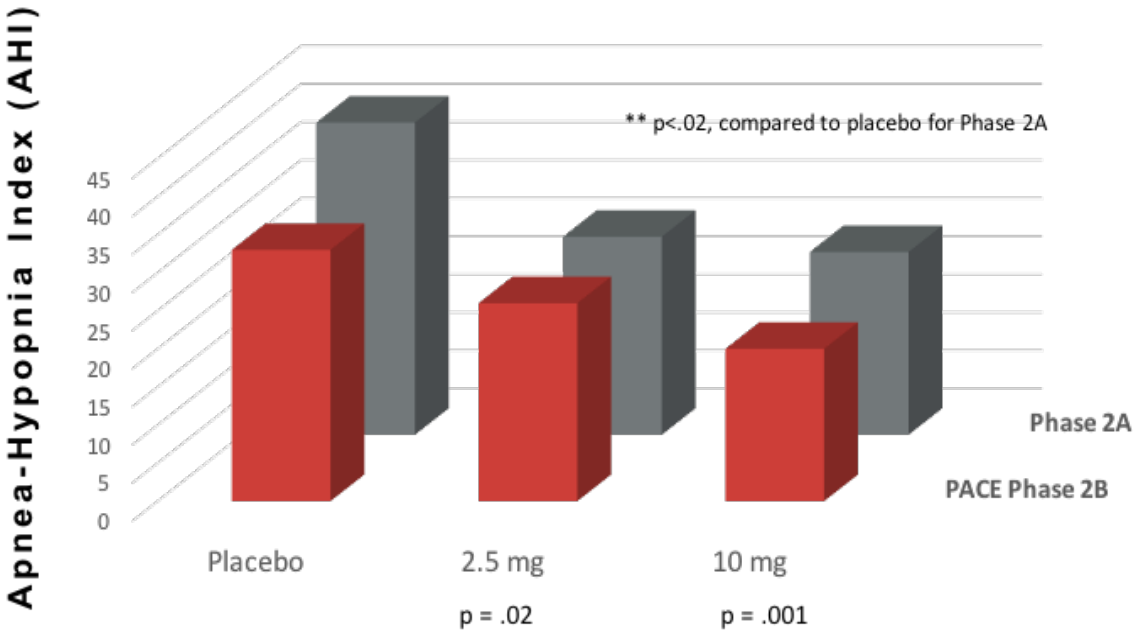


**Two Phase 2 Trials Have Shown that Dronabinol Treatment Results in a Statistically Significant, Dose Related Improvement in AHI, the Primary Endpoint for FDA Approval**

* Double blind, placebo controlled dose-ascending study in patients with OSA, 2a n=19 2b n=57

[1] Published in Frontiers in Psychiatry January 2013 | Volume 4 | Article 1

# Dronabinol Reduces Daytime Sleepiness

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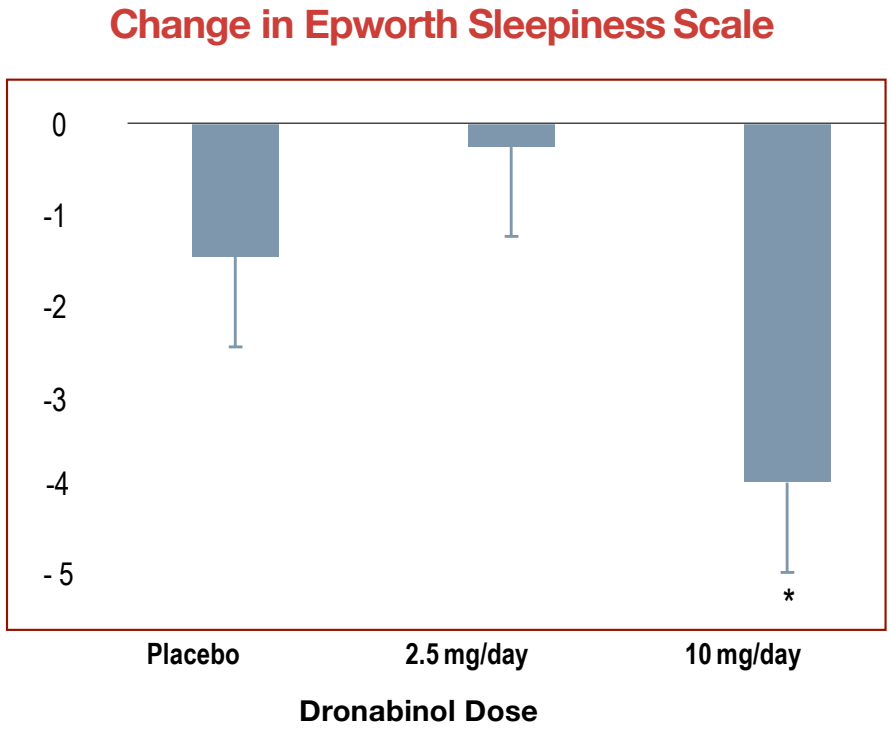


* p<0.05, compared to placebo

PACE Enhancement Cannabimimetic Apnea by Pharmacotherapy of Clinical Trial

# Dronabinol Improves MWT

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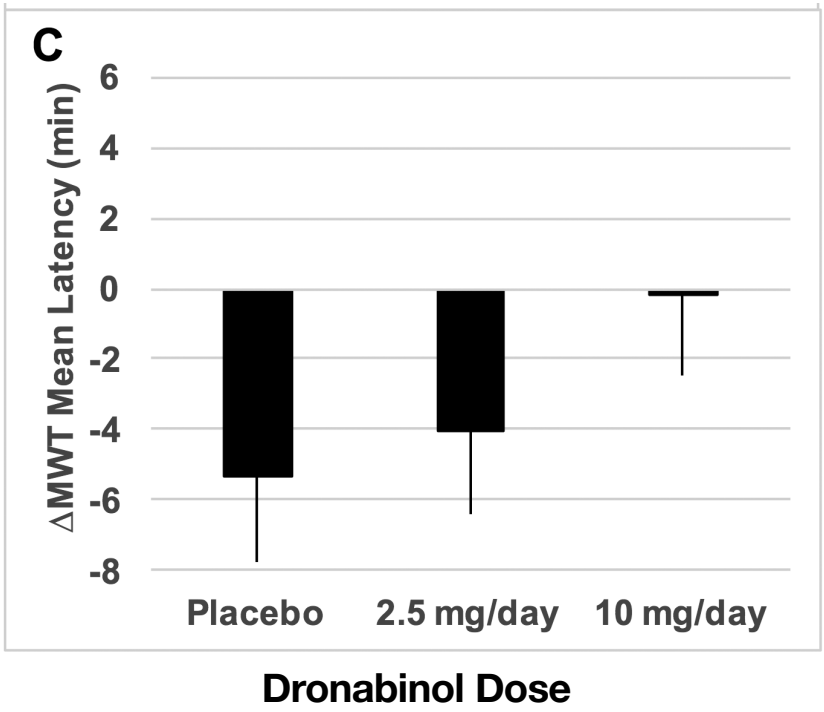
## Change in Mean Wakefulness Testing (MWT)




PACE Enhancement Cannabimimetic Apnea by Pharmacotherapy of Clinical Trial

# Dronabinol Has an Excellent Safety Profile

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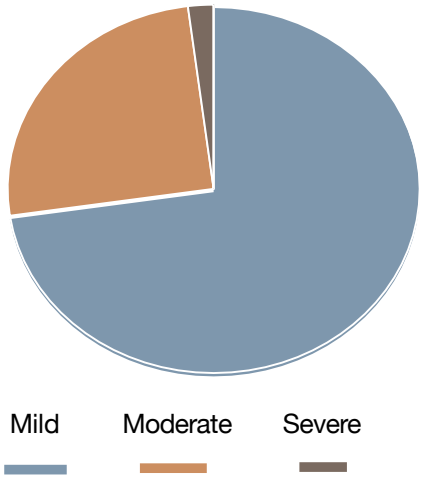
**Great Majority of AEs were mild to moderate**




- **Average Number of AEs = 4.1±4.0**
- **AEs did not differ by treatment group**
- **Most Frequent Verbatim AEs Reported Were:**
  - Sleepiness/Drowsiness (N=25)
  - Headache (N=24)
  - Nausea/Vomiting (N=23)

# *New Formulations Based on Clinical Data*

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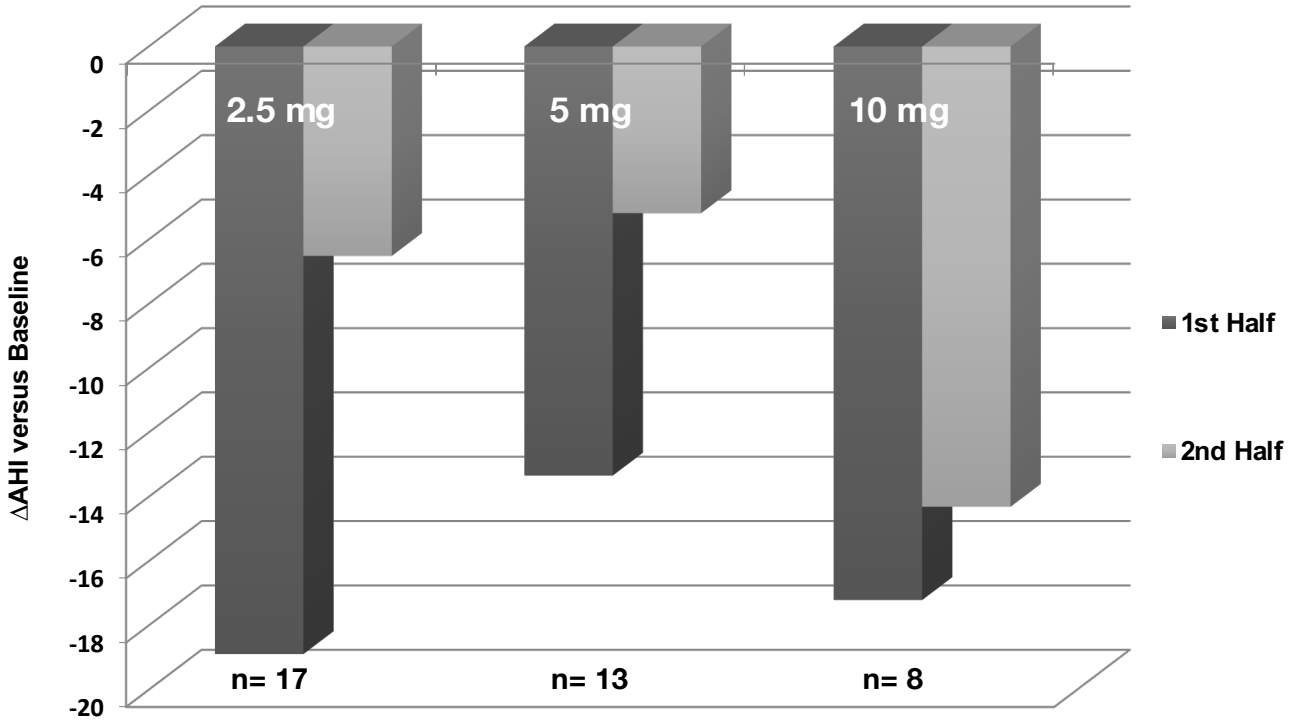
**Change in AHI in the 1st 4 hours vs. the 2nd 4 hours of the night**




The plasma half-life of dronabinol is 2 – 4 hours

- **Low dose dronabinol is as effective as the high dose in the first half of the night**
- **Effectiveness diminishes in the second half of the night**
- **Opportunities for low dose, controlled release formulations**

# Present Dronabinol Gel-cap Formulations

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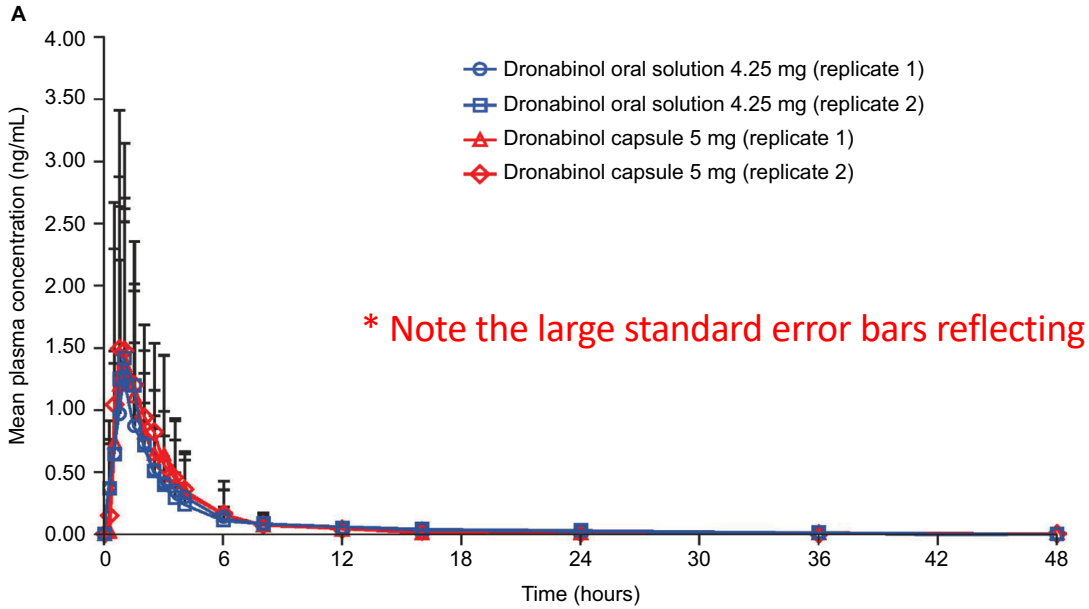
- Poor and erratic absorption, with some patients achieving very high levels and others achieving very low levels.




* Note the large standard error bars reflecting a very high variability

Parikh *et al*, Clinical Pharmacology: Advances and Applications 2016:8 155–162

# *Present Dronabinol Gel-cap Formulations*

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- Poor and erratic absorption, with some patients achieving very high levels and others achieving very low levels.
- Rapid and extensive first-pass liver metabolism, resulting in low blood levels and a relatively short half-life (approximately 3 hours) which is not optimally suited for therapeutic indications requiring blood levels to be sustained for 6 hours or longer.
- Undesirable side effects from high dosage strength required to achieve sustained, therapeutic blood levels

# Lipid-based Cannabinoid Formulations

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## *Intended Goals*

1. Soluble with appropriate dissolution
2. Particle size in the 50 - 150 nM range
3. Room temperature stability
4. Resistant to disturbance by stomach acids
5. Lymphatic absorption to bypass liver metabolism
6. Encapsulation efficiency
7. Amenable to commercial scale production

# Lipid-based Cannabinoid Formulations

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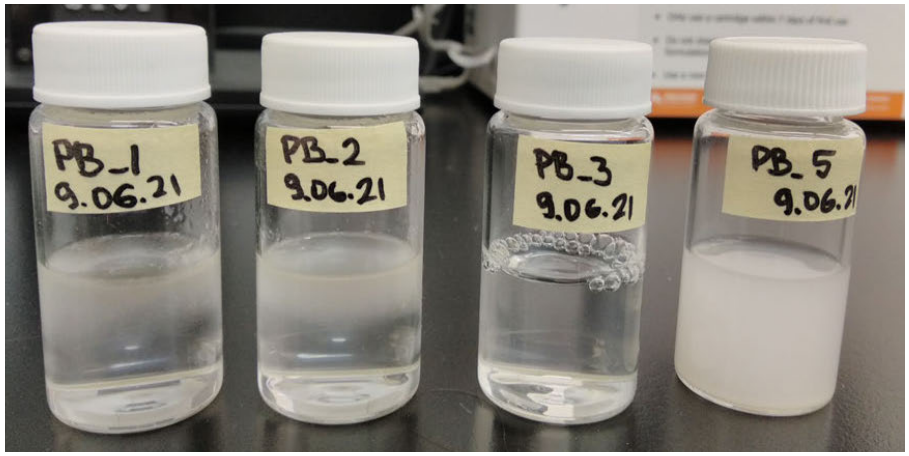


Clear, no visible phase separation

# Lipid-based Cannabinoid Formulations

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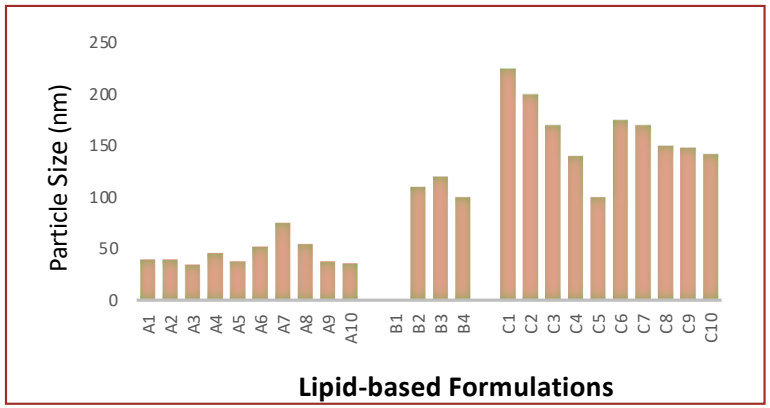


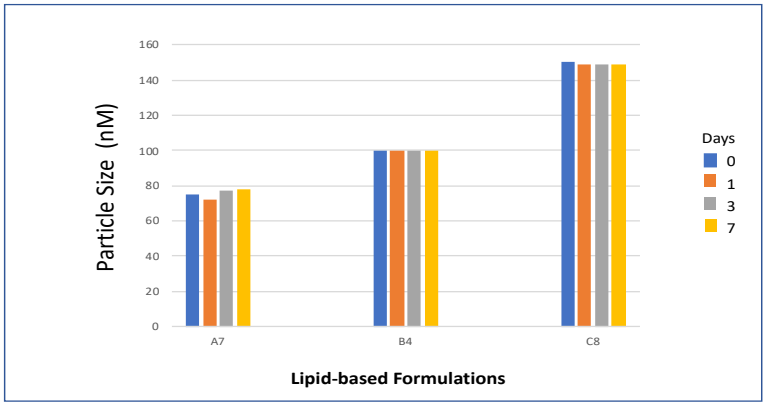


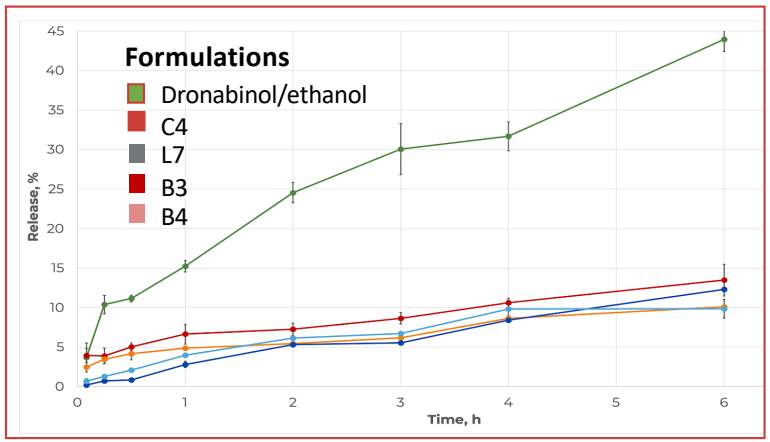


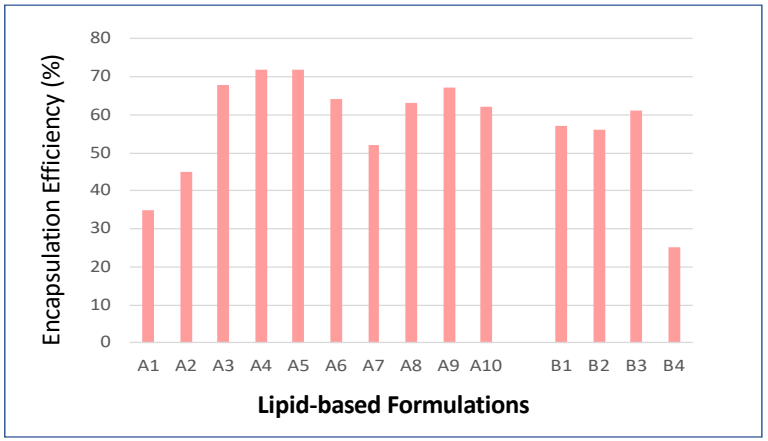

# Remaining Issues

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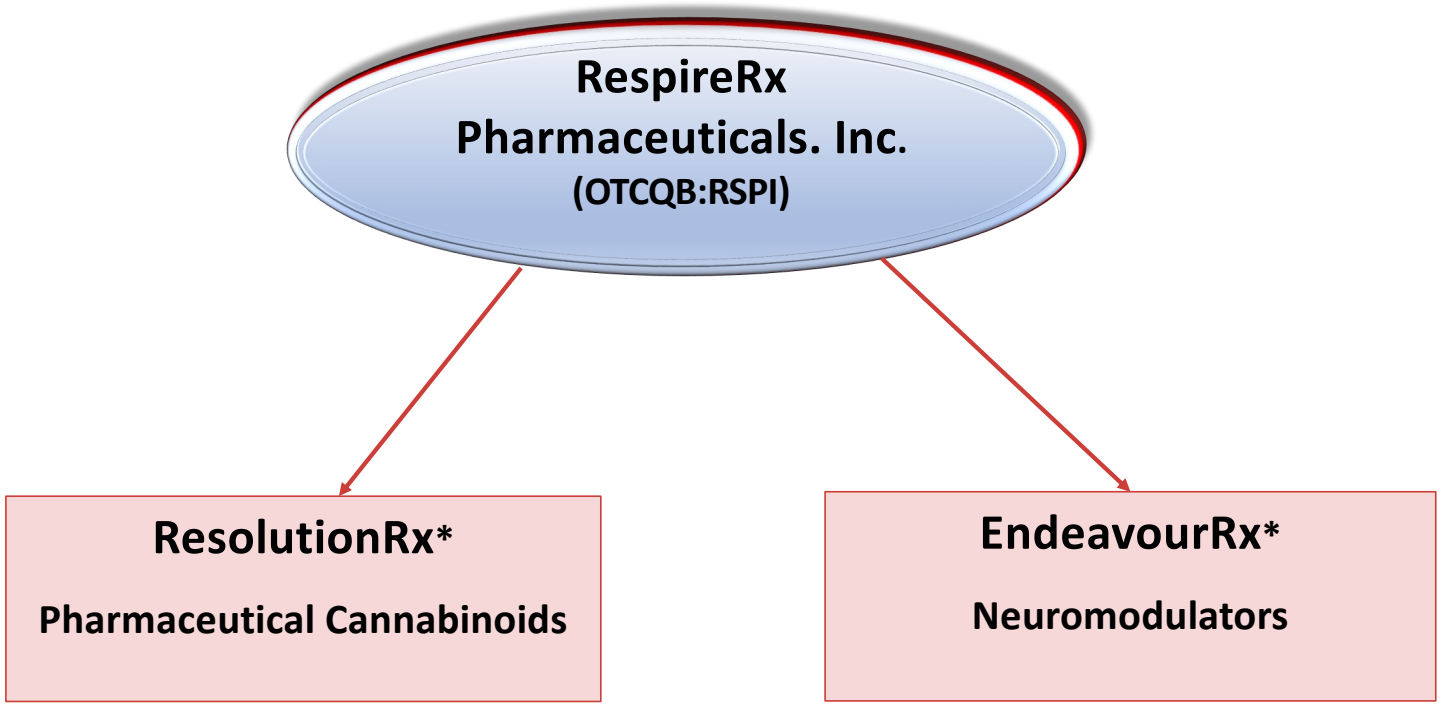
***1. Pharmacokinetics***

***2. Clinical Dosage Forms*** – partner with larger firm to create supply of clinical material.

***2. Pre-IND Meeting with FDA***

***3. FUNDING!!!!***

# RespireRx - Corporate Structure




* See respective business plans

**ResolutionRx:**
**A New Pharmaceutical Cannabinoid Business Unit of RespireRx**

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**OTC QB: RSPI**


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