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Transforming the Possible in Neuroscience

A Different Kind of Biopharma Company

July 2020

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Participants in the Solicitation. ARYA, Cerevel and their respective directors and executive officers may be deemed participants in the solicitation of proxies from ARYA's shareholders with respect to the proposed Business Combination. A list of the names of ARYA's directors and executive officers and a description of their interests in ARYA is contained in ARYA's final prospectus relating to its initial public offering, dated June 4, 2020, which was filed with the SEC and is available free of charge at the SEC's web site at www.sec.gov, or by directing a request to ARYA Sciences Acquisition Corp II, 51 Astor Place, 10th Floor, New York, New York 10003. Additional information regarding the interests of the participants in the solicitation of proxies from ARYA's shareholders with respect to the proposed Business Combination will be contained in the proxy statement/prospectus for the proposed Business Combination when available.

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Investment Highlights

- Utilizing our differentiated understanding of disease-related biology and neurocircuitry of the brain with advanced chemistry to develop novel therapies for CNS diseases
- Broad portfolio of 11 assets targeting large markets with significant unmet need, including schizophrenia, epilepsy, and Parkinson's Disease
- Progressing towards multiple near and medium-term catalysts, with 8 data readouts and multiple INDs expected over the next 3 years
- Leveraging a seasoned management team with extensive expertise in neuroscience and a strong track record of over 20 prior drug approvals and commercialization

Majority ownership

BainCapital

$350 million capital commitment

Retained ownership

Pfizer

Portfolio built on:
10+ years of research
$1 billion+ R&D investment

11 Neuroscience assets

Novel targets; small molecules

Experienced management team

Development driven by data

Led by a Seasoned Life Sciences Management Team

Tony Coles, M.D.
Chief Executive Officer & Chairperson

Raymond Sanchez, M.D.
Chief Medical Officer

Bryan Phillips
Chief Legal Officer

Kenneth DiPietro
Chief Human Resources Officer

Kathy Yi
Chief Financial Officer

John Renger, Ph.D.
Chief Scientific Officer

Orly Mishan
Chief Business Officer

Kathleen Tregoning
Chief Corporate Affairs Officer

Strong Track Record of Approvals

ABILIFY® (aripiprazole)

Abilify MyCite® (aripiprazole tablets with sensor) 2, 5, 10, 15, 20, 30 mg

Abilify Maintena® (aripiprazole) for extended release injectable suspension

Belsomra® (suvorexant) IV 5, 10, 15, 20 mg tablets

JYNARQUE® (tolvaptan) tablets

Nexavar® (sorafenib) tablets

Samsca® (tolvaptan)

Kyprolis® (carfilzomib) for Injection

REXULTI® brexpiprazole

ADHANSIA XR™ (methylphenidate HCl) II extended-release capsules

BLINCYTO® (blinatumomab) for injection

Yumanity THERAPEUTICS · NPS Pharma. · VERTEX · Bristol-Myers Squibb · NOVARTIS · Otsuka · Boston Scientific · AVANIR pharmaceuticals

ONYX PHARMACEUTICALS · Biogen · MERCK · Pfizer · GUIDANT · IMBRIUM THERAPEUTICS · PURDUE · Sangamo THERAPEUTICS

Cerevel's Differentiated Approach to CNS Disease

Highly Selective Small Molecules
Created using Pfizer world-class chemistry

→

Receptor Binding/Modulation

→

Differentiated Understanding of Neurocircuitry

Pipeline Uniquely Based on

- Targeted Receptor Subtype Selectivity
- Optimized Receptor Pharmacology
- Robust Data Packages

Deep Pipeline: Multiple Value Inflections Near & Long-Term

11 Assets

5
Clinical Assets

- Tavapadon
- CVL-865
- CVL-231
- CVL-871
- CVL-936

4
Pre-Clinical Assets

- LRRK2*
- M4 Agonist*
- PDE4B*
- KORA (CVL-354)

2
Undisclosed Assets

7 Programs

- Early Parkinson's
- Late Parkinson's
- Epilepsy
- Anxiety
- Schizophrenia
- Alzheimer's Disease Apathy
- Substance Use Disorder

8 Trials

3	Phase 3 Trials
2	Phase 2 Trials
1	Phase 1b Trial
2	Phase 1 Trials
+2	Open Label Extensions

* - Lead Optimization

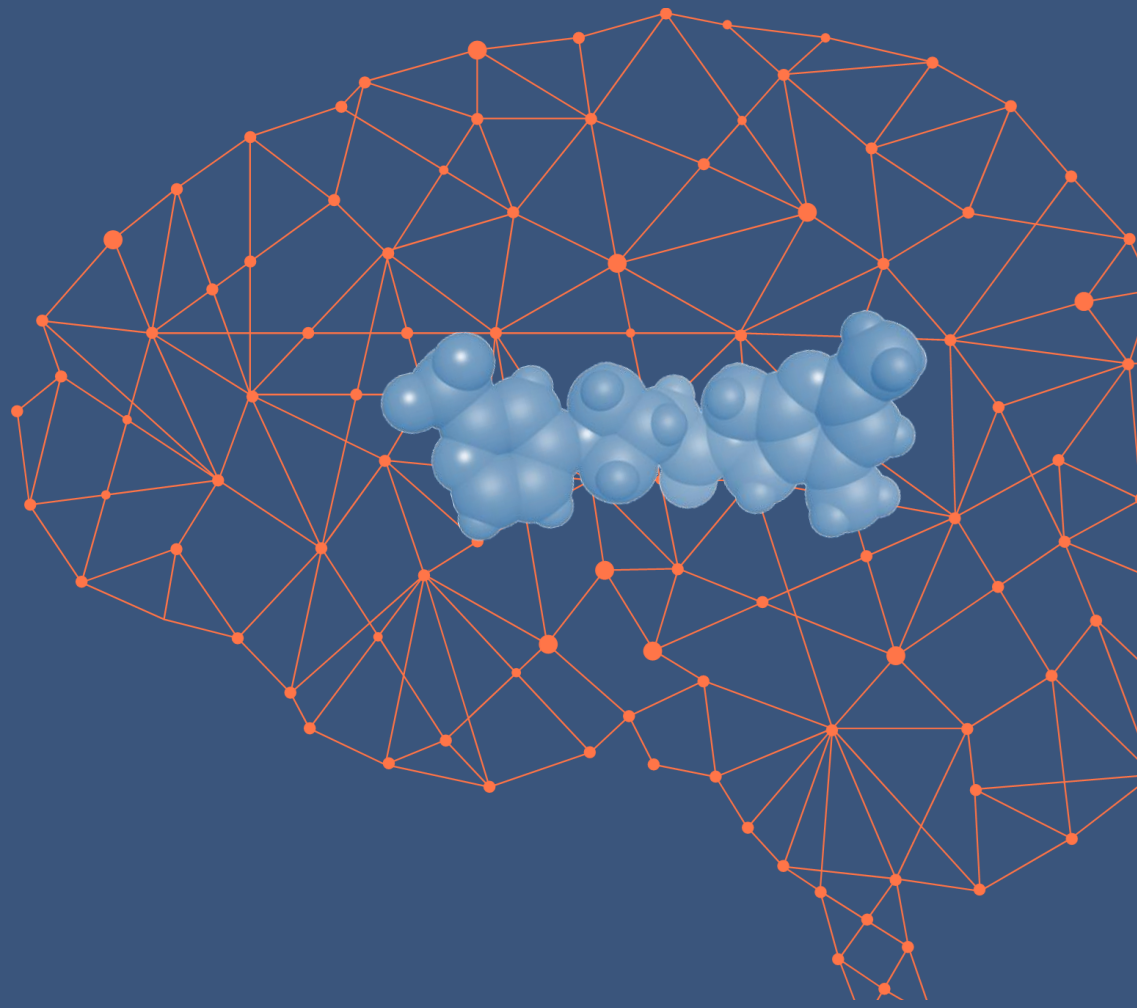
Cerevel Clinical Pipeline: Broad, Deep and Diverse

Compound	Disease Area	Discovery	Pre-clinical	Phase 1	Phase 2	Phase 3	Upcoming Milestone	Mechanism
Tavapadon	Early Parkinson's						Ph. 3 Data	**D1/D5 Strong Partial Agonist** ★
Tavapadon (adjunct with L-Dopa)	Late Parkinson's						Ph. 3 Data	
CVL-865	Epilepsy						Ph. 2 Data	**$GABA_A$ α2/3/5 PAM** ★
CVL-865	Anxiety						Ph. 1 Data	
CVL-231	Schizophrenia						Ph. 1b Data	**M4 PAM** ★
CVL-871	Alzheimer's Disease Apathy						Ph. 2 Data	**D1/D5 Partial Agonist**
CVL-936	Substance Use Disorder						Ph. 1 Data	**D3 Preferring Antagonist**

★ Asset overview included in this presentation

M4 PAM (CVL-231) in Schizophrenia

Selectively targeting the M4 muscarinic receptor with the goal of treating psychosis-related symptoms with improved side effect profile



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Cerevel's M4 PAM is a Potential Next Generation Antipsychotic

M4 PAM (CVL-231)

Potential New Standard of Care

First-in-Class Therapy with Novel MOA

M4 Selective

Targeted Muscarinic Activity

Improved Tolerability

Opportunity for Innovation in Schizophrenia

Current Standard of Care Uses Same Mechanism of Action (MOA) as Therapies from the 1950s

Large Market

- ~21M Patients Worldwide
- >$9B Revenues in 2018
- ~3.5% Growth per year

Significant Need for New Treatment Option

Side Effect and Tolerability Issues

Lead to → Limited Compliance (60%) → High Relapse Rates (77% at 1 year, 90% at 2 years)

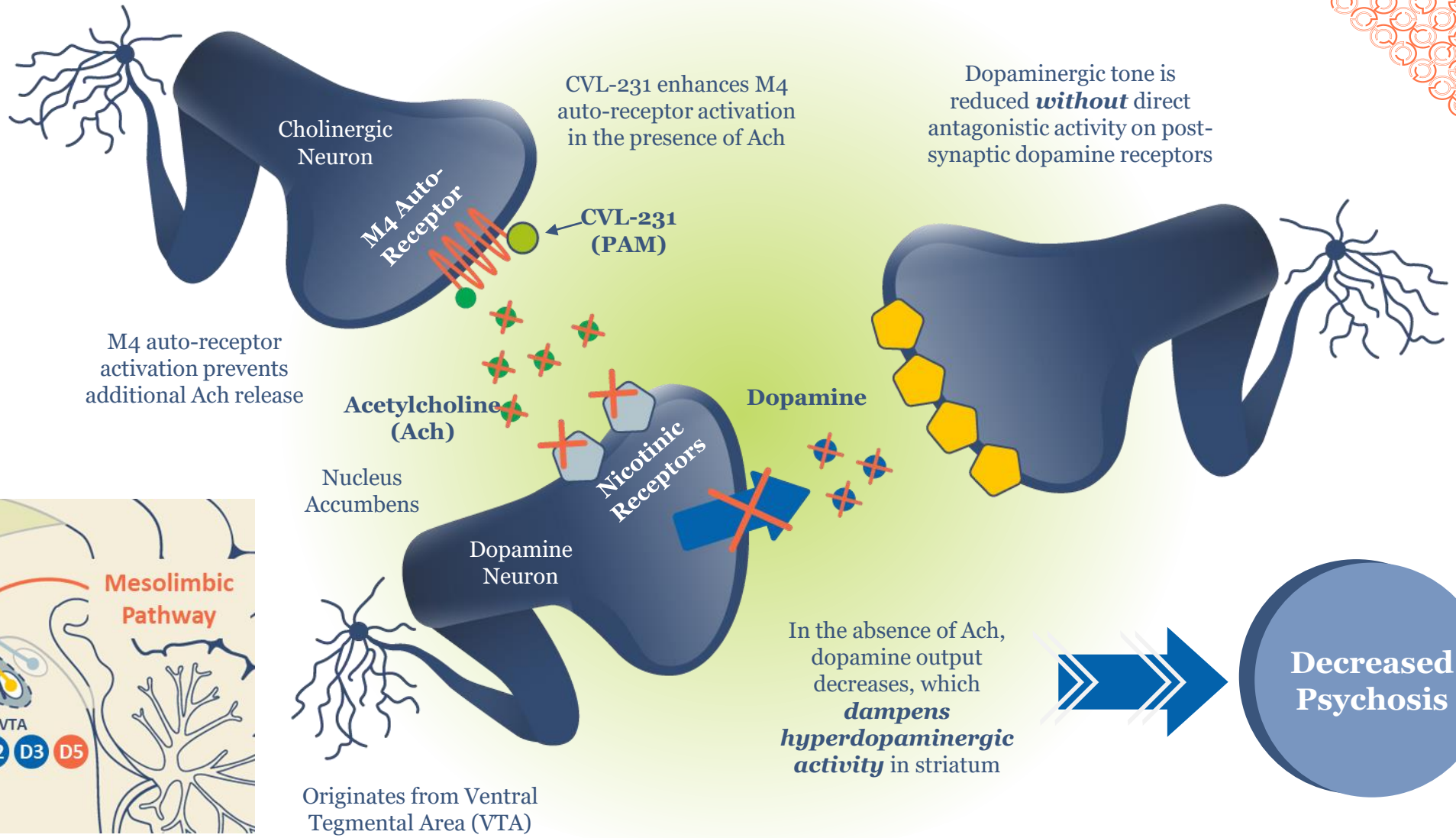
Lead to → Progression and worsening of disease

Lead to → High Discontinuation (74% Within 18 months)

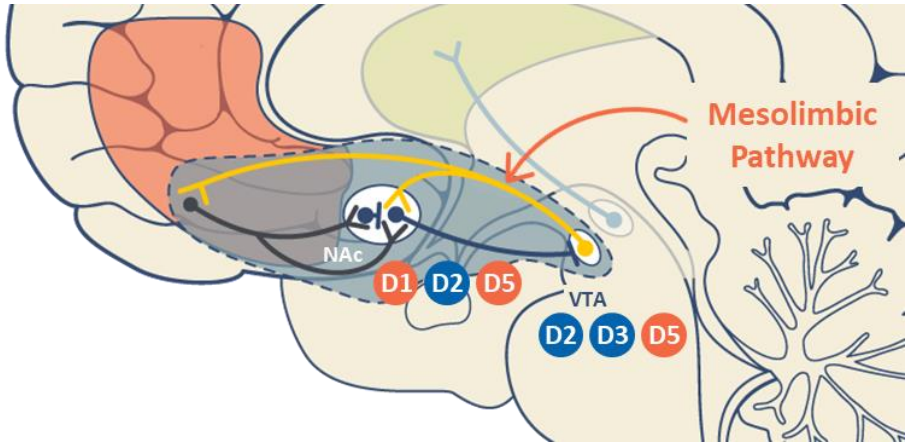
Debilitating side effects of atypicals often lead to discontinuation and relapse, driving a vicious cycle of disease progression

Source: World Health Organization, DRG Market Research

M4 Receptor Activation Reduces Dopamine in the Striatum



Schizophrenia symptoms driven by ***overactivity of the dopaminergic*** mesolimbic pathway



Cerevel's Selective M4 Modulation: A Compelling and Differentiated Approach to Drive Antipsychosis

M4 Selectively Impacts Brain Functions

Other Muscarinic Receptors	Potential Effect	M4 Muscarinic Receptor
-	Antipsychosis	✓✓
✓✓	Cognition	✓
✓✓	GI Side Effects	-
✓	Cardiovascular	✓

Receptor Subtype Selectivity Offers Potential Improvement

Xanomeline (M1/M4) data from Schizophrenia and Alzheimer's patients show targeting muscarinic receptor impacts brain function

But development limited by GI and CV side effects

Karuna's KarXT creatively addresses this by adding trospium to Xanomeline to offset side effects

Non-selective approach

M4 Knock-out mouse data suggests M4 receptors drive the antipsychotic activity of Xanomeline

M1 receptors believed to contribute to worrisome side effects

CVL-231:
Highly Selective Once-daily (QD) M4 PAM

>800x
more selective for M4 over M1, 3 and 5

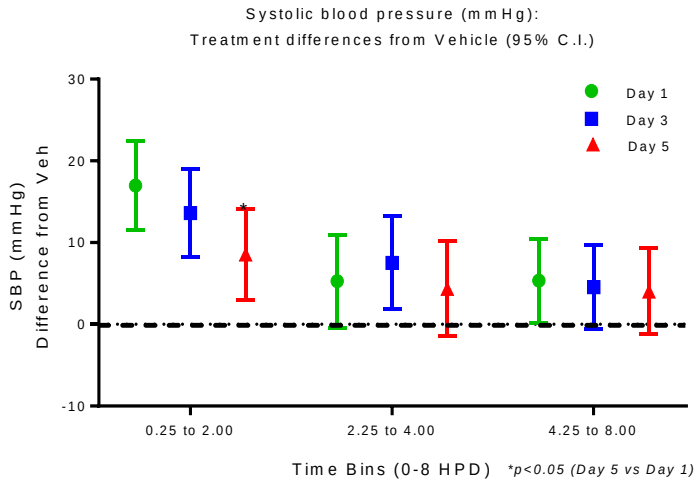
>390x
more selective than for M2

Source: 1. Shekhar et al. Am J Psychiatry, Vol 165, Aug 2008. N=20. 2 active and 3 placebo-arm patients discontinued the study, none due to adverse events.
2. Bodick et al. Arch Neurol, Vol 54, Apr 1997. N = 343. 52% of patients in high-dose arm discontinued treatment due to adverse events.

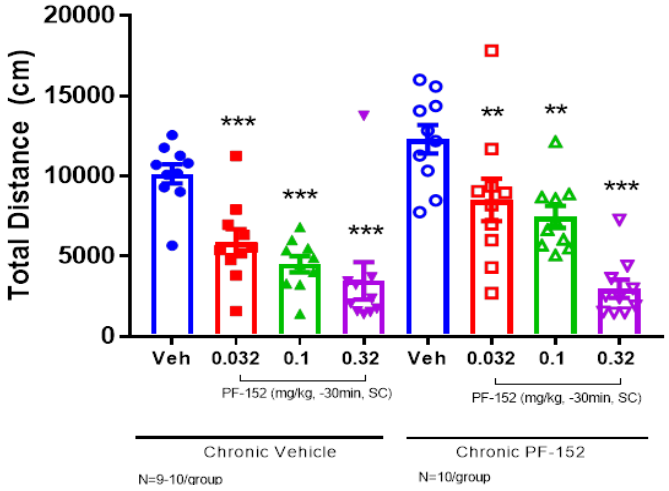
Cardiovascular Effects may be Attenuated with Titration and Repeat Dosing

Repeated dosing of M4 Agonist Tool in rodents showed attenuation of cardiovascular effects without impact on antipsychotic activity; in addition, CVL-231 showed attenuation of heart effects in a 3-month canine toxicology study

5-Day repeat dosing of M4 Agonist Tool: Attenuation of Blood Pressure Effects in Mice



14-Day repeat dosing of M4 Agonist Tool: No Attenuation of Antipsychosis in Mice



3-Month Study of CVL-231: Attenuation of Heart Rate Effects in Canines

- On Day 1, observed heart rate increases were statistically significant and outside normal range
- On Days 43 and 90, heart rate increases were small and not statistically significant; all mean heart rate values were within normal range and not considered adverse

Clinical translation: KarXT showed an average increase in resting heart rate of 5.5 beats per minute with a downward trend after the second week

M4 PAM Ongoing and Planned Studies - Data Expected 2H21

Study 001 – Phase 1b

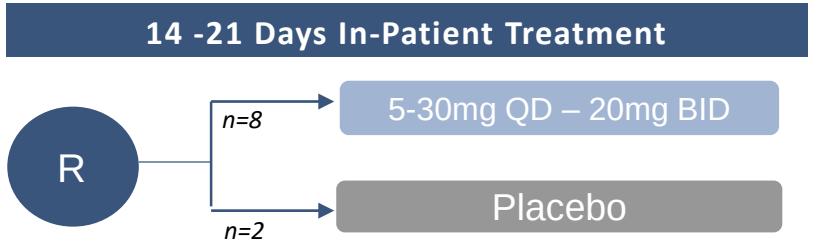
Part A: Safety Assessment

Multiple Ascending Dose

Primary Objective
- Safety & tolerability

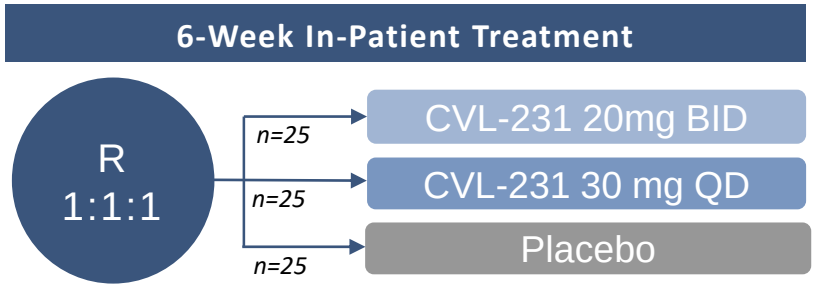
Secondary Objective
- PK

Up to 5 Cohorts (n=10 each)



Part B: Pharmacodynamics

Exploratory PD Assessment
- Positive and Negative Syndrome Scale (PANSS)*
- Clinical Global Impression – Severity Scale (CGI-S)*
- Brief Assessment of Cognition in Schizophrenia (BACS) symbol coding test*



PET Studies

Study 002 – Phase 1b

Single Dose (n=9)

Designed to inform PK vs. target receptor occupancy

Study Objectives	**Primary** M4 CNS receptor occupancy vs. peripheral drug exposure	**Secondary** Safety and tolerability

Study 003 – Phase 1b

Single Dose (n=9)

Designed to inform receptor occupancy vs. target pharmacology

Study Objectives	**Primary** Modulation of striatal levels of dopamine with CVL-231	**Secondary** Safety and tolerability

Methodically developed to identify optimal PK and PD for Phase 2 trial

* Not powered for statistical significance

Dementia-Related Psychosis (DRP): Potential Opportunity for CVL-231 Beyond Schizophrenia

DRP Overview and Unmet Needs[1-7]

- Psychosis incidence ranges from 10-75% of Alzheimer's patients and varies by stage of disease
  - Upwards of 1M moderate to severe Alzheimer's patients in the G7 experience symptoms of psychosis
- Co-morbidities including agitation, aggression and depression
- Contributes to increased caregiver burden
- Often leads to long-term care / nursing home admissions

Standard of Care

- Off-label use of atypical antipsychotics: tolerability issues heightened in this population; contribute to cognitive decline
- One molecule in clinical studies is currently being evaluated in the treatment of DRP

Next Steps for CVL-231

- CVL-231 side effects / tolerability observed to date are appropriate for further clinical evaluation in elderly patients
- 2021 Clinical Pharmacology study in the elderly

1) Biol Psychiatry. 2014 April 1; 75(7): 542–552. 2) J Prev Alz Dis 2018: Pimavanserin in AD psychosis: Efficacy in patients with more pronounced psychotic symptoms. 3) Ballard, C., Gauthier, S., Cummings, J. et al.. Nat Rev Neurol 5, 245–255 (2009) 4) Sultzer et al., (2004) 5) Flint et al., (1991) 6) Sultzer et al., (1992) 7) Paulsen, et al. Incidence of and risk factors for hallucinations and delusions in patients with probable Alzheimer's disease. Neurology. 2000; 54:1965–1971

Potential Indications for M4 PAM Beyond Schizophrenia

Pipeline in a Pill

Goal to be a novel MOA and next generation treatment in Schizophrenia

Aiming for a Side Effect and Tolerability Profile Appropriate for Chronic Use in Elderly Populations

Potential Large Indications Worldwide

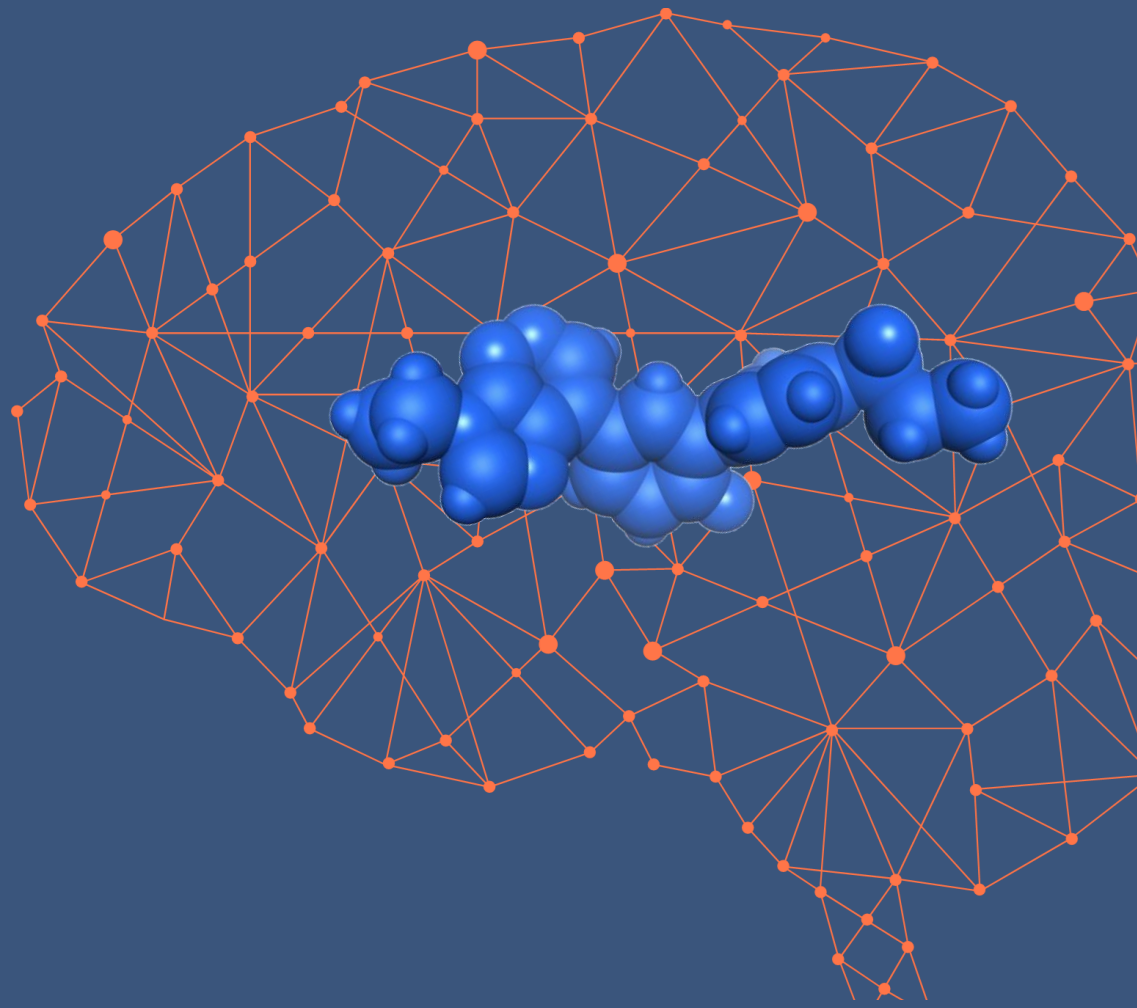
Schizophrenia	~21M Patients
Alzheimer's Psychosis	~20M Patients
Cognition	>50M Patients
PD-LID	~5M Patients

Potential to expand use outside of core schizophrenia population to behavioral and psychological symptoms of dementia

Source: DRG Market Research reports, World Health Organization

GABA PAM (CVL-865) in Epilepsy

Selectively targeting the α-2/3/5 subunits of the GABA receptor with the goal of enhancing anti-convulsive effects without dose-limiting sedation



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Cerevel's GABA PAM has Potential for Benzo-like Activity, Improved Side Effects and Chronic Dosing

GABA PAM (CVL-865)

Potential to become first-line and adjunct therapy

Targeted GABA α 2/3/5 Receptor Selectivity

Benzo-like Activity

Improved Tolerability

Potential for Reduced Abuse Liability

Opportunity for New Treatment Option in Epilepsy

HCPs and patients are dissatisfied due to insufficient activity, side effects and poor tolerability

Large Market

- ~65M Patients Worldwide
- >$6B G7 Revenues in 2018
- ~6% per year Branded AED[1] Market Growth through 2025

Benzos are highly efficacious, but…

- Poor Tolerability
- Desensitization & Loss of Efficacy
- Potential for Abuse
- Withdrawal

Potential as chronic therapy with improved side effect profile and tolerability may expand use vs. traditional benzodiazepines

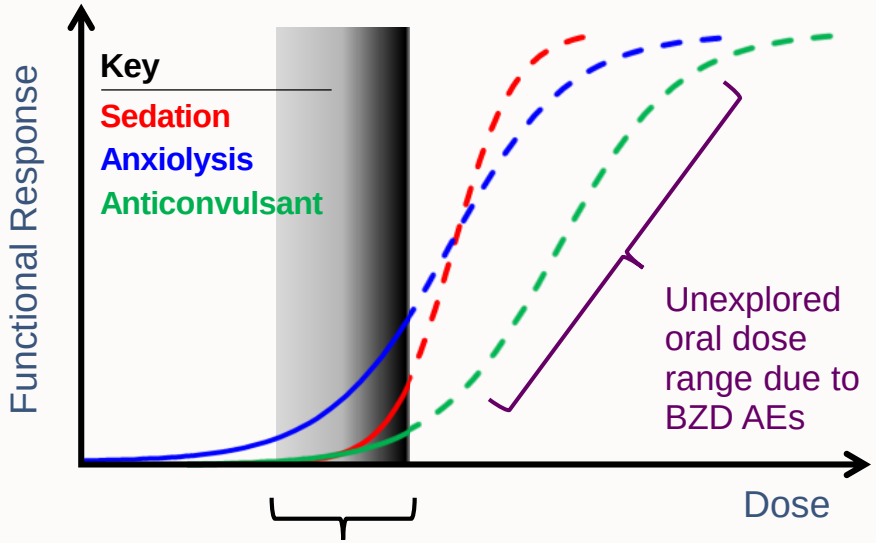
Source: World Health Organization, DRG Market Research

1. AED: Anti-Epileptic Drug

The Problem With Benzodiazepines (abridged…)

- BZDs are efficacious in a range of indications but use and dose is limited by adverse events, even at low receptor occupancy
  - Sedation, somnolence, cognitive impairment, falls, overuse, misuse and addiction
- In epilepsy, loss of efficacy can develop quickly with BZDs which limits their use
- BZDs can be difficult to withdraw once use is established, and can be associated with further AEs

Clinical experience with BZDs



Dose range for oral classical BZDs limited by sedative AEs
(<20% receptor occupancy)

Selective $GABA_A$ Receptor PAM: Potential for Lower Seizure Rates, Reduced Side Effects

GABA α-2/3/5 Can Differentially Address Symptoms

CVL-865

GABA subtype predicted effects:	α1	α2	α3	α5
Anti-convulsant	✓✓	✓✓		
Anxiolysis		✓✓	✓✓	
Analgesia		✓✓	✓	✓✓
Muscle Relaxation		✓✓	✓✓	
Sedation	✓✓			
Cognitive Impairment	✓✓	?	?	✓
Addiction	✓✓	✓		

Benzodiazepine side effects

Role for Targeted GABA α 2/3/5 Receptor Selectivity

- >10 benzodiazepines (BZDs - broad-spectrum GABA modulators) widely prescribed for anxiety, seizures and other indications
- Significant need for better-tolerated, less sedating and less addictive GABA modulators
- BZD Rx's increased >95% from 2003-2015

To our knowledge, CVL-865 is the only GABA α-2/3/5 selective PAM in clinical trials for epilepsy

GABA PAM Data Showed a Favorable Side Effect Profile Relative to Benzodiazepines

Multiple doses of CVL-865

Phase 1 MAD Study – only mild AEs and limited somnolence up to 42.5 mg BID

Able to achieve >80% receptor occupancy without significant somnolence observed whereas Benzodiazepines achieve 10% to 15% receptor occupancy with significant somnolence observed

No evidence of withdrawal effects

Phase 1 MAD Study (Protocol: B7431011)

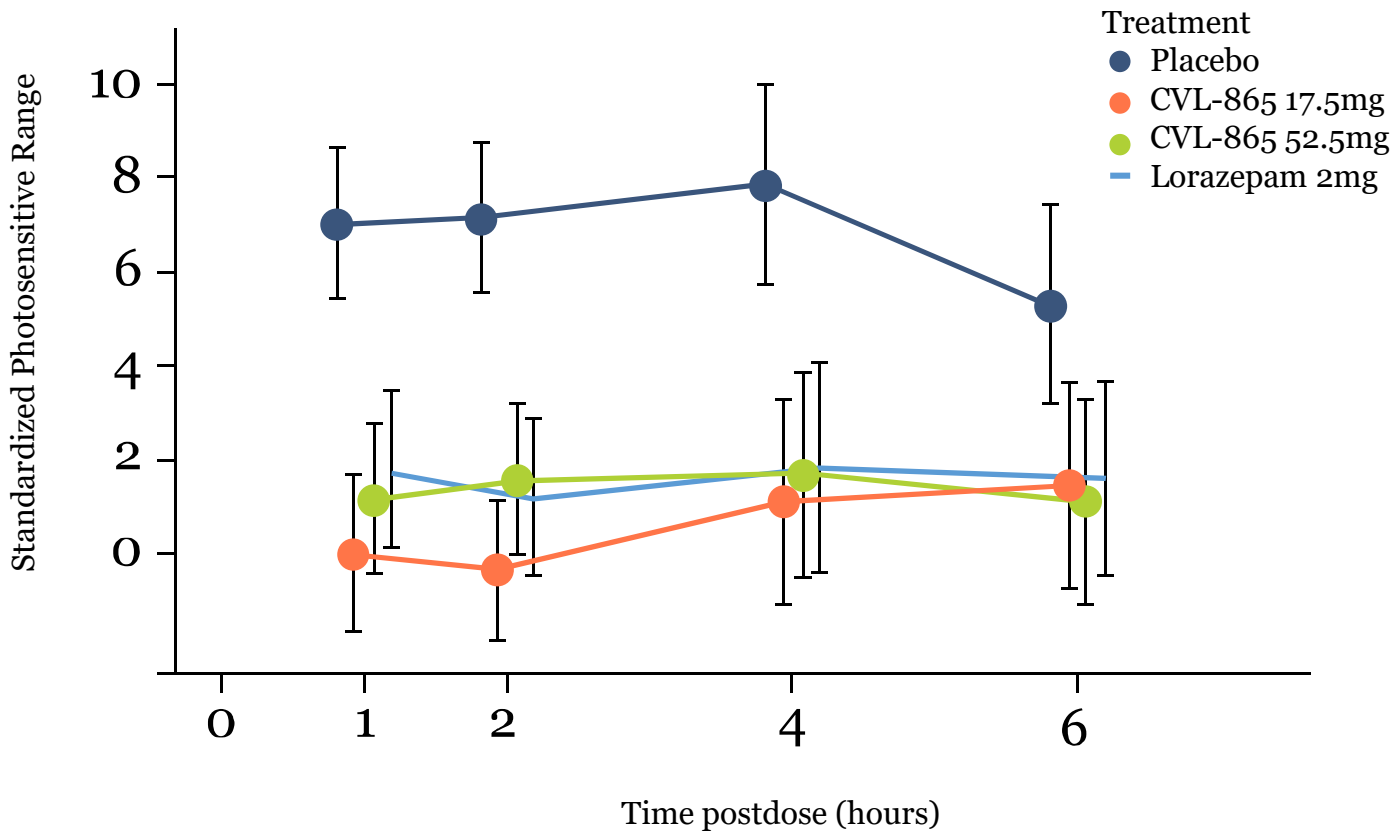
	Reaction	Week 1 (Titration)	Week 2 (Maintenance)	Week 3 (Maintenance)	Follow-up
Placebo	**No Reaction**	**4 / 4**	**4 / 4**	**3 / 4**	**4 / 4**
	Dizziness	-	-	1 / 4	-
	Somnolence	-	-	-	-
25 mg BID (~80% RO[1])	**No Reaction**	**5 / 8**	**7 / 8**	**8 / 8**	**8 / 8**
	Dizziness	2 / 8	1 / 8	-	-
	Somnolence	3 / 8	-	-	-
42.5 mg BID (>80% RO[1])	**No Reaction**	**4 / 7**	**6 / 7**	**6 / 7**	**6 / 7**
	Dizziness	3 / 7	1 / 7	1 / 7	1 / 7
	Somnolence	-	-	-	-

No somnolence observed following titration through doses of 42.5 mg BID

(1) Receptor Occupancy

GABA PAM Phase 2 Data Showed Benzo-like Anticonvulsant Activity in Photosensitive Epilepsy[1]

CVL-865 in Single-Dose Photosensitive Epilepsy Study



CVL-865

Anticonvulsant activity comparable to lorazepam

Improved sedation and AE profile compared to benzos

Complete suppression in 6 of 7 subjects

Majority of AEDs developed for epilepsy that showed positive published photoepilepsy results were approved[2]

Source: (1) IND B7431005: Phase 2 double-blind, randomized, cross-over study using lorazepam as a positive control; n=7 photoepilepsy subjects per arm; (2) Yuen and Sims. Seizure 23 (2014) 490–493

GABA PAM Phase 2 Design in Focal Onset Epilepsy Data Expected 2H22

CVL-865 Phase 2 Program In Epilepsy

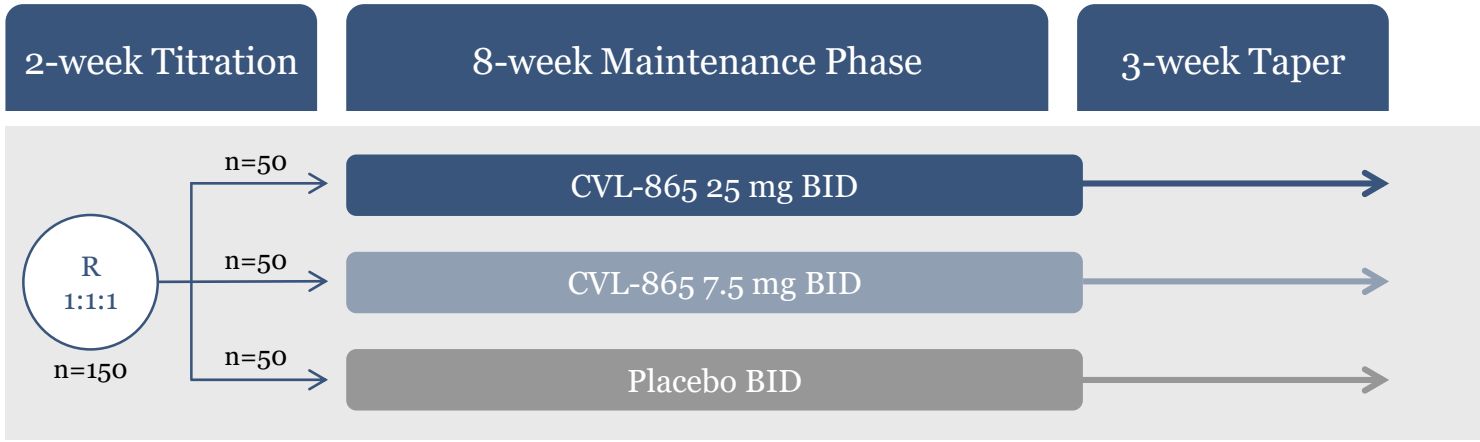
Targeting ~60 sites in 4 countries

Inclusion criteria

- Adults (18-75) with drug-resistant focal onset epilepsy
- History of 4+ seizures per month for at least 3 months
- 1-3 stable background AEDs allowed

Primary endpoint

- Reduction in focal onset seizure frequency



Patients able to join 57-week open-label extension trial after completion of 8-week maintenance phase

Focal onset epilepsy intended to establish proof of concept and side effect profile to support development in broader epilepsy indications

Potential Indications for GABA PAM Beyond Epilepsy

Pipeline in a Pill

Potential for benzo-like activity with targeted GABA α 2/3/5 receptor selectivity

Benzos (Non-selective GABA Modulators) Widely Prescribed for Seizures, Anxiety, and Other Indications

Potential Large Indications Worldwide

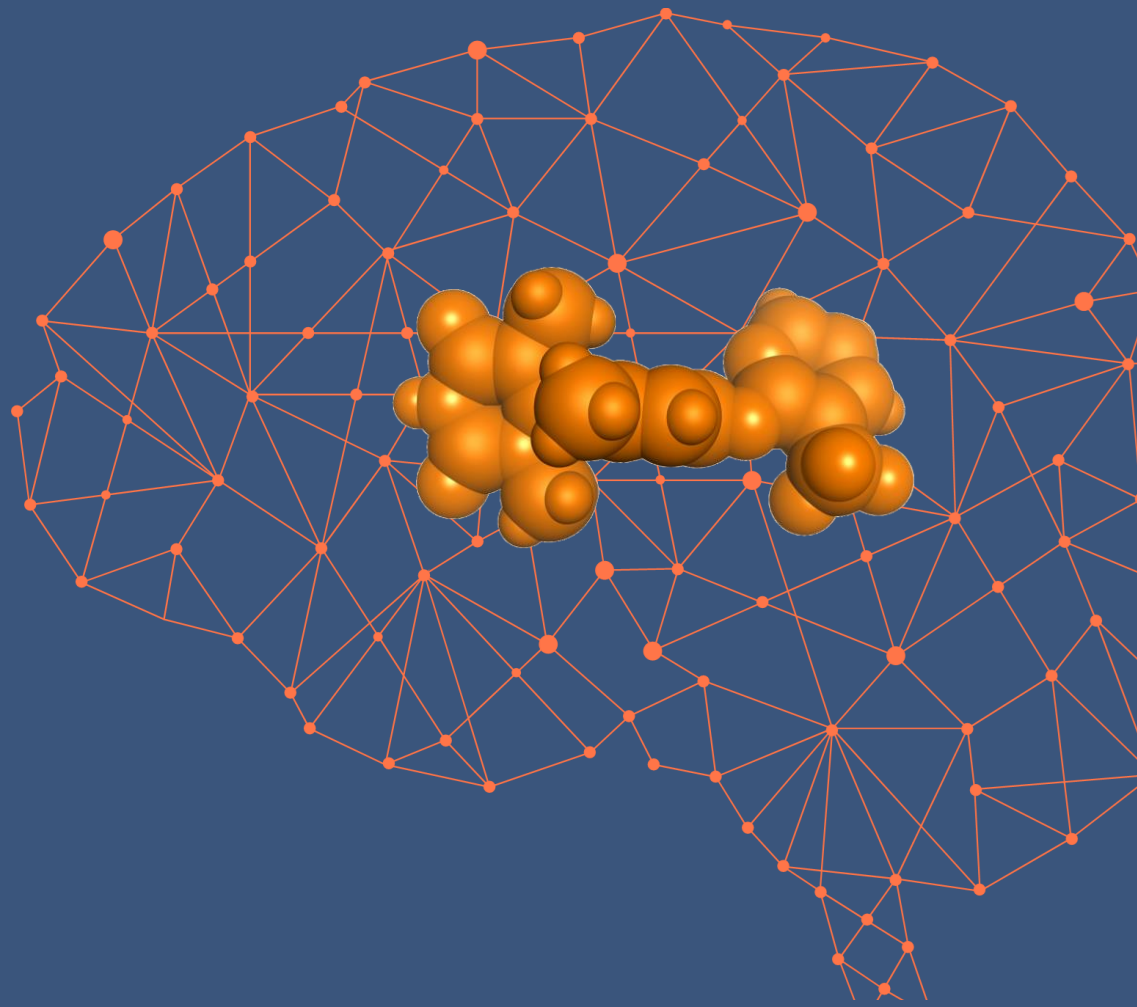
Epilepsy	~65M Patients
Anxiety Disorders	~13M Patients (G7)
Agitation	15-20M Patients
Bipolar Disorder	~46M Patients

Significant need for GABA modulators that are better tolerated, less sedating, less addictive and supportive of chronic use

Source: DRG Market Research reports, World Health Organization

Tavapadon in Parkinson's Disease

Partial agonist selectively targeting the dopamine D1 receptor with the goal of enhancing motor control while minimizing side effects



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Tavapadon has Potential to be a Differentiated Treatment for Parkinson's

Designed to be a novel backbone therapy for patients from diagnosis to the end of treatment:

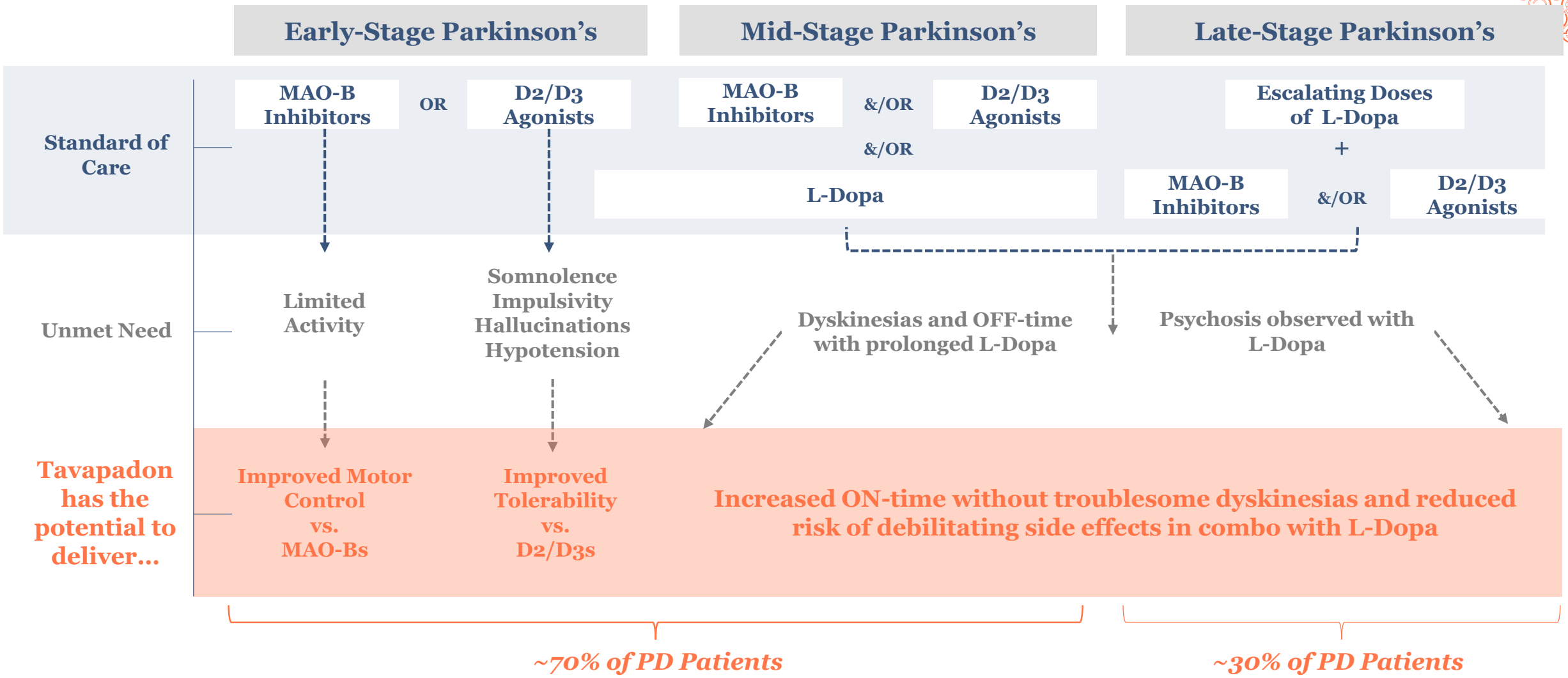
Only* D1/D5 selective molecule	**Avoid D2/D3 Side Effects:** *Sudden daytime somnolence, hallucinations, acute orthostasis and impulse control disorders*
First* partial agonist for Parkinson's	**Avoid Dyskinesias:** *Driven by receptor overexcitation*
Predictable 24-hour activity	**Sustained Effect:** *Once daily, oral dosing*
Selective direct motor pathway activation	**Superior motor control over D2/D3s full agonists**

- Feedback received from FDA on our registrational program (2019)
  - Two of our three Phase III studies initiated earlier this year, currently paused due to COVID-19
- To our knowledge, nothing else in the symptomatic pipeline positioned to provide broad therapeutic benefit and differentiation

→ First-in-class potential designed to offer stable motor control and favorable side effect profile with broad monotherapy and adjunct therapy benefit

* To our knowledge

Tavapadon Designed to Address Unmet Needs Across All Stages of Parkinson's: Early and Late

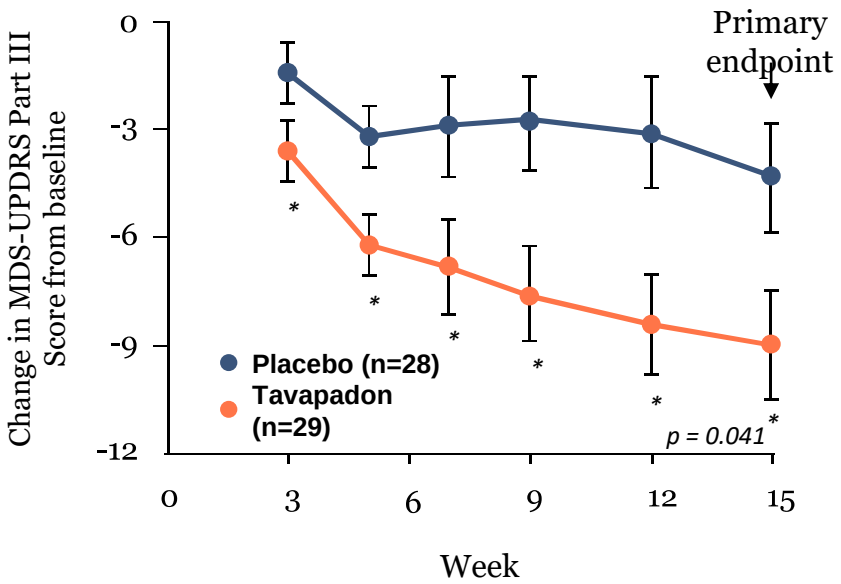


Source 1. PD MED Collaborative Group. Lancet 2014; 384: 1196–205.
Source 2. Ahlskog JE, Mov Disord 16:448–458

Selective Direct Motor Pathway Activation Designed to Provide Differentiated Treatment Option in Early Parkinson's

Potential for motor control as good or better than D2/D3s with once-daily dosing and improved side effect profile

Phase 2 Data: Tavapadon in Early PD[1]
(Primary Endpoint: MDS-UPDRS III Motor Score)



In Phase 2, tavapadon demonstrated 4.8 point MDS-UPDRS III difference vs. placebo at week 15 (p=0.04, MMRM)

Note: Average dose of tavapadon = 9 mg; 11 patients on 15 mg top dose at week 15. Baseline Part III scores of 24.3 (tavapadon) and 25.8 (placebo).

Additional Tavapadon Phase 2 Data[1]

- When adjusted to exclude patients with baseline MDS-UPDRS II of 0 or 1, **showed improvement of ~2 points over placebo on MDS-UPDRS Part II**[2]
- Most common AEs included headache and nausea (can be mitigated with titration)
- Incidence of known D2/D3 side effects:
  - Somnolence: 14%
  - Nausea: 31%
  - Hallucinations: 0%[3]
  - Hypotension-Related Events: 7%
  - Dizziness: 7%

Tavapadon demonstrated 5.8 point improvement over placebo at week 15 on MDS-UPDRS Part II + III (p = 0.02, MMRM)

1. Study B7601011: (n=57) 15-week, Phase 2, double-blind, randomized, placebo-controlled flexible dose study to investigate the efficacy, safety, and tolerability of Tavapadon in subjects with early stage Parkinson's Disease Primary endpoint: Change from baseline in the MDS-UPDRS Part III total score at week 15. Allowed concomitant MAO-B inhibitors 2. Excluding 8 participants (6 treatment, 2 placebo) with baseline MDS-UPDRS Part II scores of 0 or 1 resulted in an improvement on MDS-UPDRS II at week 15 of -2.4 points for the tavapadon arm (n=19) vs -0.6 points for the placebo arm (n=20), resulting in a placebo-adjusted difference of 1.8 points (raw data, completers at week 15). Raw data placebo-adjusted difference is 1.3 points (including 8 participants). 3. Also observed 0% hallucinations in late-stage PD Phase 2 study B7601003 as adjunct to l-dopa

Ongoing Registration-Enabling Global Phase 3 Program

Three Phase 3 trials optimally designed to maximize treatment effect

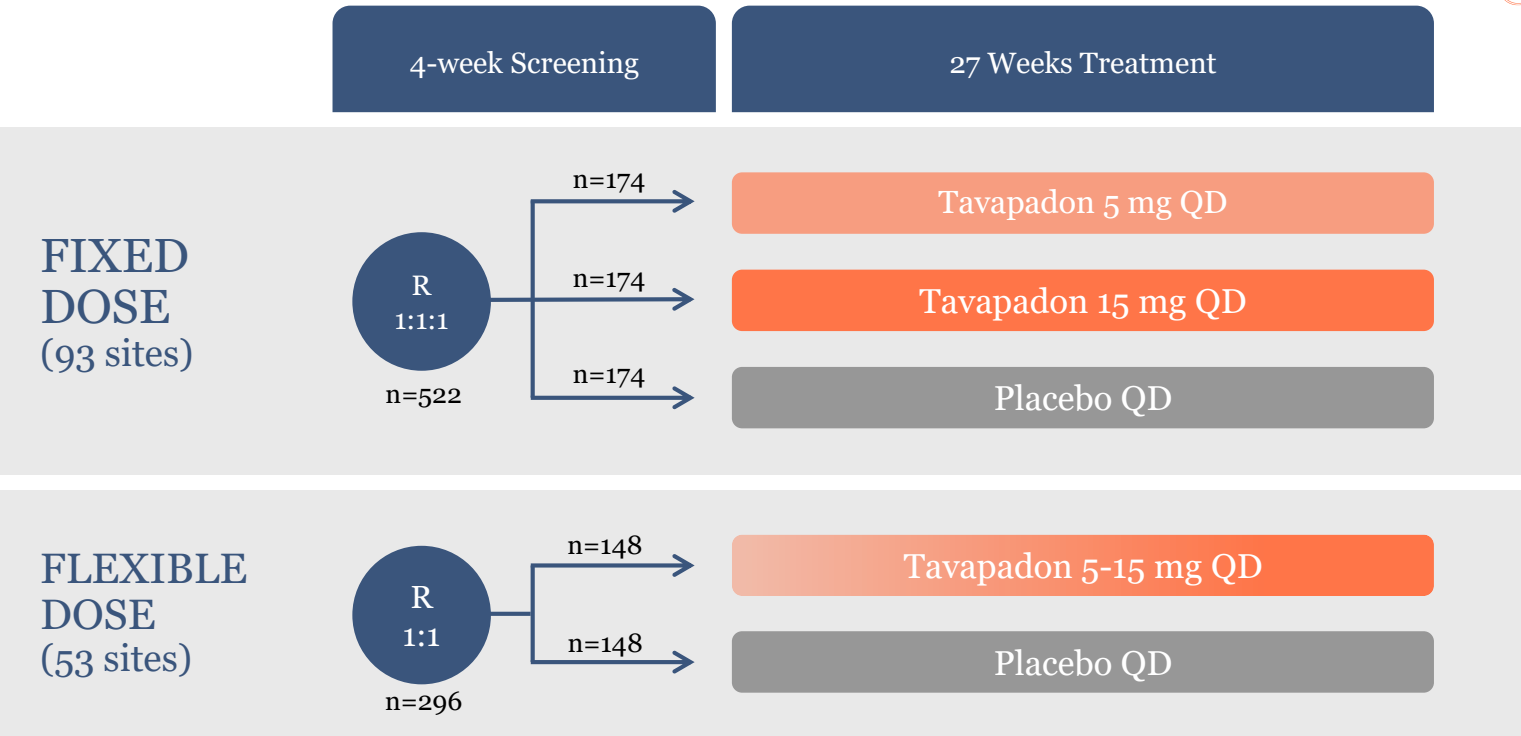
Early PD: Data Expected 2H23

Key inclusion criteria

- Adults 40-80 years old
- Baseline MDS-UPDRS[1] Part III Score ≥10 and Part II Score ≥2
- Modified Hoehn & Yahr[2] stage 1 to 2
- No concomitant meds except MAO-B inhibitors

Primary endpoint

- Change in MDS-UPDRS Parts II+III



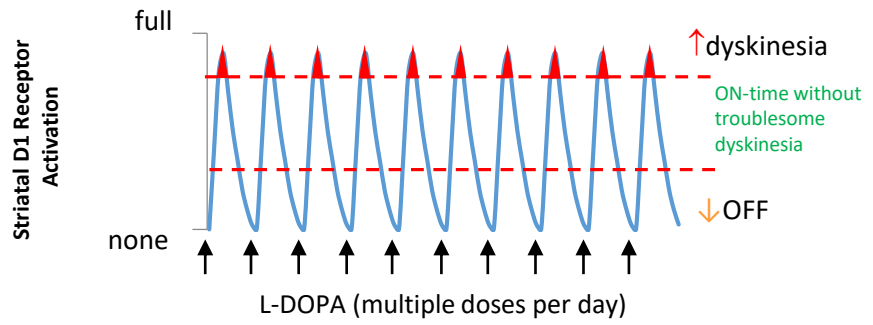
(1) MDS-UPDRS – Movement Disorder Society Unified Parkinson's Disease Rating Scale
(2) Hoehn & Yahr – staging system for characterizing the progression of symptoms for Parkinson's Disease
Note: All studies will include an open-label extension, which will further support the safety database

Predictable 24-hour Activity ➔ Sustained Effect: Once Daily, Oral Dosing

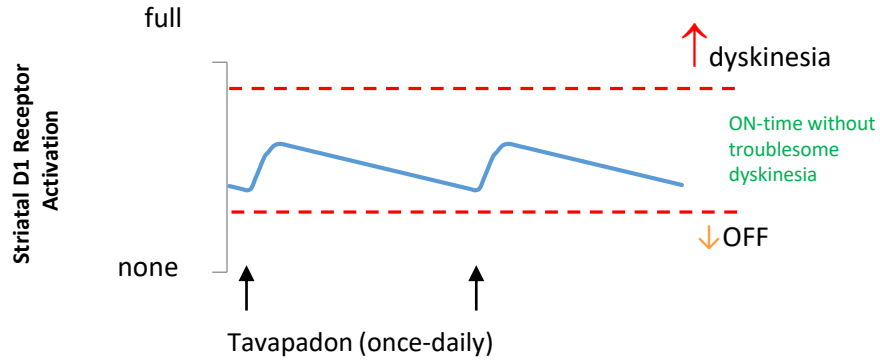
Phase 1B: Sustained Motor Control on par with L-Dopa

L-Dopa vs. Tavapadon in Late-Stage PD[1]

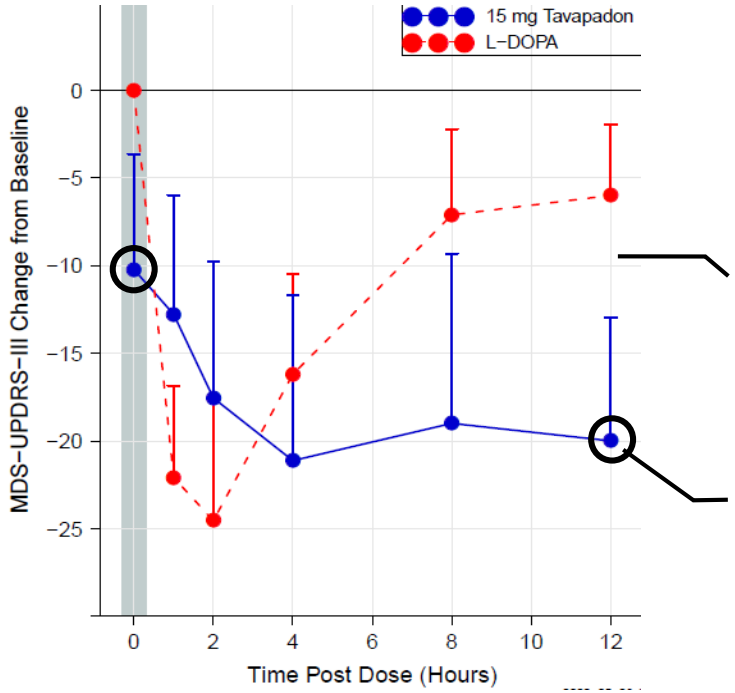
L-Dopa is a **FULL** agonist with **SHORT** half-life



Tavapadon is a **PARTIAL** agonist with **LONG** half-life



Study 1005: Tavapadon in Late-Stage PD[2]



Designed to provide sustained motor benefit during crucial morning wake period…

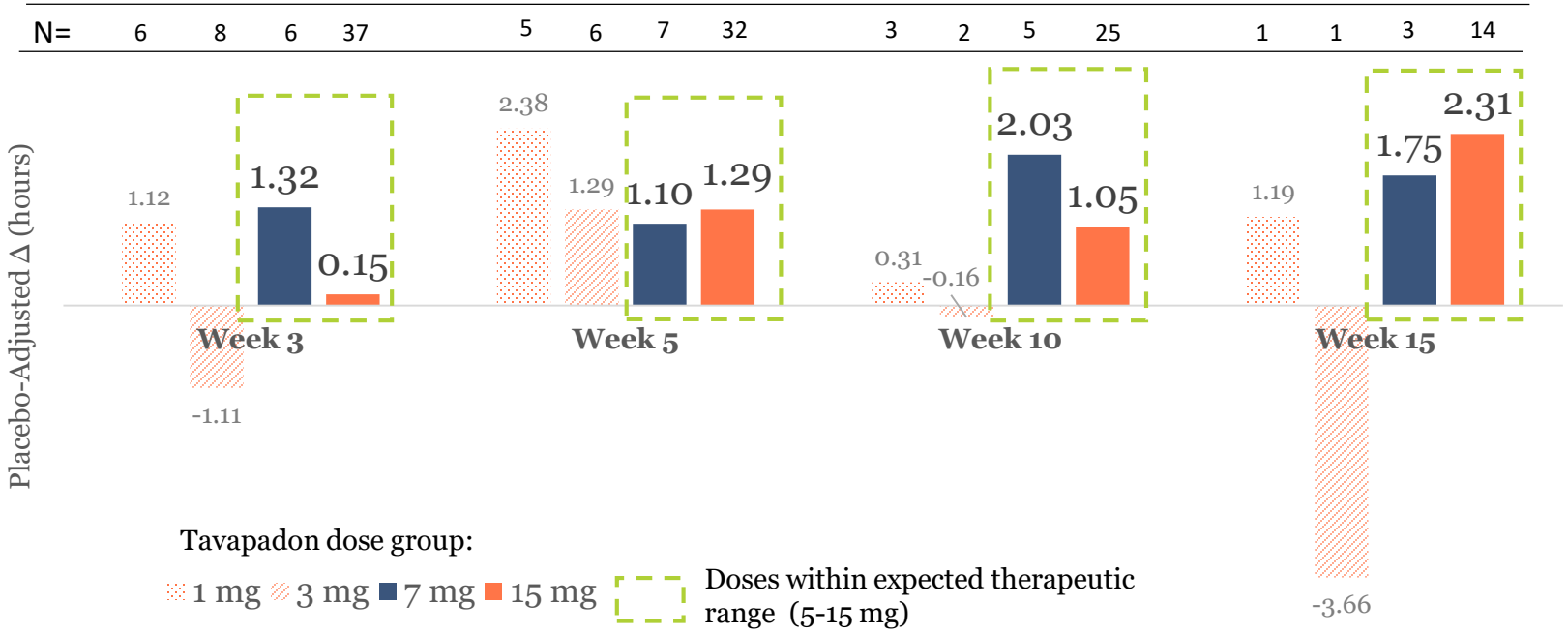
… and throughout the day

In an open-label Phase 1b trial, tavapadon demonstrated motor improvement on par with L-Dopa, sustained due to its 24-hour half-life

1) Bastide ME, et al. Prog Neurobiol. 2015;132:96-168
2) Study B7601005: (n: l-dopa arm= 50, 15 mg = 11). One-sided 90% CI. Phase 1b, two-period open label dose escalation study in patients with Parkinson's disease and motor fluctuations. In period 1 of the study, l-dopa responsiveness was assessed. In period 2, levodopa was washed out and tavapadon was dosed QD over 21 days

Tavapadon Phase 2 Results: Clinically Meaningful ON-Time without Troublesome Dyskinesias

Tavapadon generally demonstrated at least 1 hour of improvement in ON-time without troublesome dyskinesias in late-stage PD



Note: Tavapadon showed -0.6 hour reduction on the primary endpoint, change in OFF-time at week 10

Tavapadon showed clinically meaningful benefit within therapeutic dose range of 5 mg to 15 mg

Trial was terminated early based on results of interim analysis for the primary endpoint of reduction in OFF-time compared to placebo at week 10.

Ongoing Registration-Enabling Global Phase 3 Program

Three Phase 3 trials optimally designed to maximize treatment effect

Late PD: Data Expected 1H23

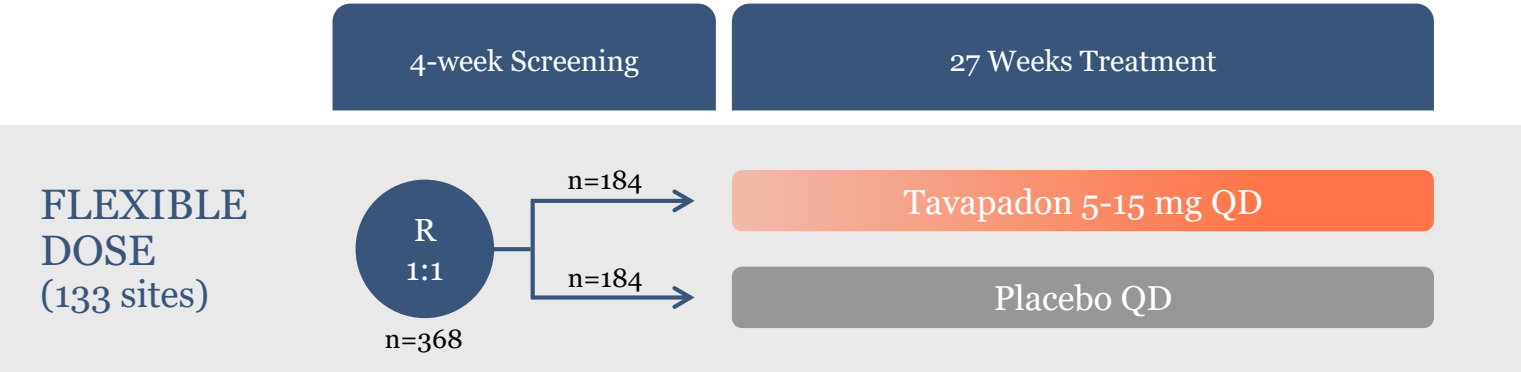
Adjunct to levodopa

Key inclusion criteria

- Adults 40-80 years old
- At least 2.5 hours OFF-time on 2 consecutive days at baseline
- Modified Hoehn & Yahr[1] stage 2 to 3, with response to L-Dopa

Primary endpoint

- Change in ON-time without troublesome dyskinesia



(1) Hoehn & Yahr – staging system for characterizing the progression of symptoms for Parkinson's Disease
Note: All studies will include an open-label extension, which will further support the safety database

Tavapadon Commercial Potential in Parkinson's

Tavapadon Target Profile

- Novel D1/D5 mechanism
- Potential similar or better motor control[1]
- Potential favorable side effect profile[2]
- 1x Once-daily dosing

Pricing & Launch

Branded US price analogs $8-10K+/year

Payor research supports broad Medicare and Commercial coverage at price of $8K+ /year

Strong side effect profile and motor control differentiation would reduce reimbursement restrictions

Patients and physician research supports acceptability of branded co-pays for a tavapadon-like differentiated profile

Differentiated profile supports pricing comparable to branded market leaders which have broad reimbursement

(1) As demonstrated by two Phase 2 studies in late (Study 1003) and early stage PD (Study 1011) and a Phase 1b in advanced PD (Study 1005);
(2) As demonstrated consistently across 272 subjects across nine clinical trials (four Phase 1 trials, two Phase 1b trials and three Phase 2 trials)

Transforming the Possible in Neuroscience

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Expected Portfolio Timeline

Compound	Mechanism	Phase / Disease Area	2020 1H	2020 2H	2021 1H	2021 2H	2022 1H	2022 2H	2023 1H	2023 2H	2024 1H	2024 2H
CVL-231	M4	Phase 1b / Schizophrenia	*									
CVL-865	GABA	Phase 1 / Anxiety										
CVL-865	GABA	Phase 2 / Epilepsy	*									
Tavapadon	D1	Phase 3 / Early PD	Fixed Dose (CVL-751-PD-001)									
			* Flex Dose (CVL-751-PD-002)									
Tavapadon *(adjunct with l-dopa)*	D1	Phase 3 / Late PD										
CVL-871	D1	Phase 2a / Alzheimer's Disease Apathy										
CVL-936	D3	Phase 1 / Substance Use Disorder										

∗ Trial paused and expected to restart in 2H20

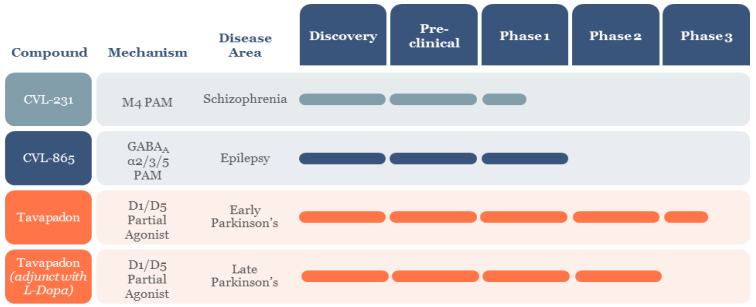
◇ Estimated Trial Initiation ◆ Estimated Topline Data

Cerevel is Transforming Possibilities for Tomorrow

Multiple Programs Aimed at Providing New Options for Millions of Patients

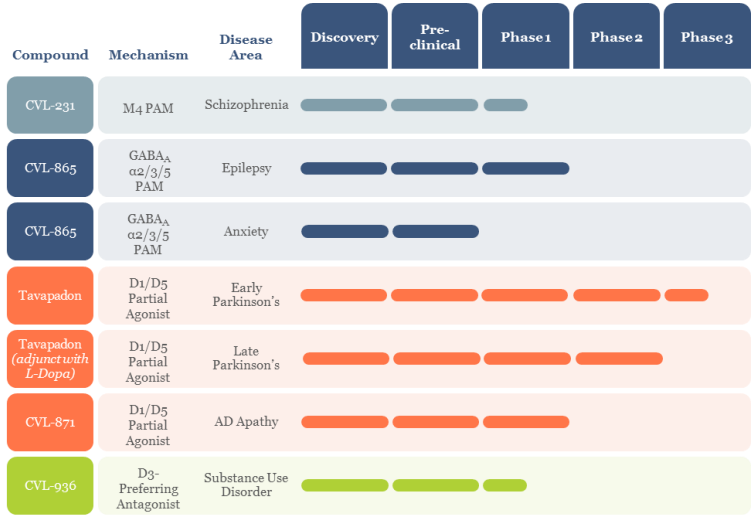
Tangible near-term value creation

- Schizophrenia
- Epilepsy
- Parkinson's



Expansion to other diseases

- Alzheimer's Psychosis
- Anxiety
- Apathy
- Substance Abuse Disorder



Long-term discovery efforts

Disease-modifying therapies based on human genetics and novel targets addressing:

- Neuronal loss
- Synaptic health

50M+ Patients WW ⊕ 100M+ Patients WW → Premier Neuroscience Company

Summary

Three Lead NCEs Across Five Clinical Programs

- **M4 PAM** (CVL-231) in **Schizophrenia**: Selectively targeting the **M4 muscarinic receptor**
- **GABA PAM** (CVL-865) in **Epilepsy and Anxiety**: Selectively targeting **GABA receptor α-2/3/5 subunits**
- **Tavapadon** in **Early- and Late-Stage Parkinson's Disease**: Potential first-in-class **D1/D5 selective partial agonist**

Upcoming Milestones

- Phase 1b study of M4 PAM (CVL-231) (data expected 2H21)
- Phase 1 study of GABA PAM (CVL-865) in Anxiety (data expected 2H21) and a Phase 2 study in Focal Onset Epilepsy (data expected 2H22)
- Three Phase 3 studies of Tavapadon in Early- and Late-Stage Parkinson's (first data readout expected 1H23)
- Multiple additional assets with INDs expected to enter the clinic in the next 24 months

Differentiated Knowledge of the Brain

- Unique understanding of disease-related receptor biology
- Focus on targeted receptor selectivity and molecules with sophisticated pharmacology
- Focus on disease areas with high unmet medical need and large commercial opportunities

Deep Pipeline Backed by Decades of Innovative Research

- 11 small molecule programs with 5 clinical compounds and 7 clinical programs
- Robust data packages supporting potential clinical differentiation

Experienced Team of Executives and Clinical Developers

- Have collectively driven over 20 drug approvals including: Abilify, Rexulti, Plavix, and Kyprolis

Cerevel and ARYA II to Combine

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Combination with ARYA II – Transaction Summary

Transaction Summary	▪ Cerevel Therapeutics, Inc. ("Cerevel") and ARYA Sciences Acquisition Corp II ("AYRA II", Nasdaq: ARYB) to merge pursuant to a business combination agreement to be entered into between ARYA II and Cerevel ◦ Cerevel is a clinical-stage biopharmaceutical company that combines a deep understanding of the biology and neurocircuitry of the brain with advanced chemistry and central nervous system (CNS) receptor pharmacology to discover and develop new therapies ◦ ARYA II is a special purpose acquisition company sponsored by Perceptive Advisors ▪ Expected post-transaction equity value of c.$1.3 billion, assuming ARYA II share price of $10 / share and no redemptions from the ARYA II shareholders ▪ Transaction expected to close in Q4 2020
Premier Specialist Investor Base	▪ Provides Cerevel with premier investor base and resources to continue executing on its development plan. Key investors of Cerevel are currently Bain Capital and Pfizer ▪ Shareholders of the combined company expected to include current Cerevel and ARYA II shareholders as well as top-tier biotech / life sciences investors, including Perceptive
Use of Proceeds	▪ Post-closing, the combined company is expected to have c.$445 million in cash, including expected proceeds from the c.$320 million PIPE financing ◦ Proceeds to fund Cerevel's R&D programs, including its M4 PAM (CVL-231) in schizophrenia, its GABA PAM (CVL-865) in anxiety and epilepsy, its D1 partial agonist (tavapadon) in Parkinson's and its earlier-stage clinical programs ◦ Expected to provide runway into 2023
Key Management and Board	▪ Combined company to be led by Cerevel Chief Executive Officer & Chairperson, Tony Coles, M.D.

Terms of Transaction

Shares and $ in thousands (other than share price)

Pro Forma Valuation

Pro Forma Shares Outstanding		129,187
Implied Share Price	$	10.00
PF Equity Value	$	1,291,865
Less: PF Cash	$	(444,500)
Plus: PF Debt	$	-
Implied PF Enterprise Value	**$**	**847,365**

Sources of Funds [1,3]

Cash Held in Trust	$	149,500
Cerevel Shareholder Equity Rollover	$	780,000
PIPE Proceeds[2]	$	320,000
Total Sources of Funds	**$**	**1,249,500**

Uses of Funds [1]

Equity Issued to Cerevel Shareholders	$	780,000
Estimated Transaction Fees & Expenses	$	25,000
Remaining Cash (Balance Sheet)[3]	$	444,500
Total Uses of Funds	**$**	**1,249,500**

Pro Forma Ownership[3]

	Shares	%
ARYA II Sponsor (Perceptive)	7,237	6%
Sponsor Shares	*4,237*	*3%*
PIPE Shares	*3,000*	*2%*
Public Shareholders[3] (excl. ARYA II Sponsor)	14,950	12%
Current Cerevel Shareholders	78,000	60%
PIPE Investors [4] (excl. ARYA II Sponsor)	29,000	22%
Total	**129,187**	**100.0%**

(1) As per closing anticipated in Q4 2020; (2) Includes $25 million pre-funding from Bain to meet Cerevel operational needs prior to closing in exchange for Cerevel shares, which shares will reduce Bain's PIPE commitment by an equal amount and will be converted into ARYA II shares on the same terms as the PIPE; (3) Assumes no shareholder redemptions and based on implied share price of $10 per share. Does not include an aggregate of 5,150 warrants outstanding with an exercise price of $11.50 per share. (4) Includes 10,000 Bain and 1,200 Pfizer shares.

Use of Proceeds

- Approximately $445 million[1] of post-transaction cash projected on the combined company balance sheet to pursue Cerevel's research and development programs
  - Expected to provide cash runway into 2023

- Projected proceeds will be primarily used to fund Cerevel's research and development programs, including:
  - Approximately $30 to $40 million to fund its M4 PAM (CVL-231) through its Phase 1b readout in schizophrenia
  - Approximately $55 to $65 million to fund its GABA PAM (CVL-865) through its Phase 1 readout in anxiety and its Phase 2 readout in epilepsy
  - Approximately $140 to $150 million to fund its D1 partial agonist (tavapadon) through its Phase 3 program in Parkinson's
  - Approximately $15 to $20 million to fund its earlier-stage clinical programs, including its D1 partial agonist (CVL-871) in apathy in patients with Alzheimer's dementia and its D3 preferring agonist (CVL-936) in substance use disorder

(1) Projected cash balance including cash held in trust, expected cash on Cerevel's balance sheet, expected PIPE financing of $320 million, assuming no shareholder redemptions or warrant exercises and including transaction costs.

Appendix

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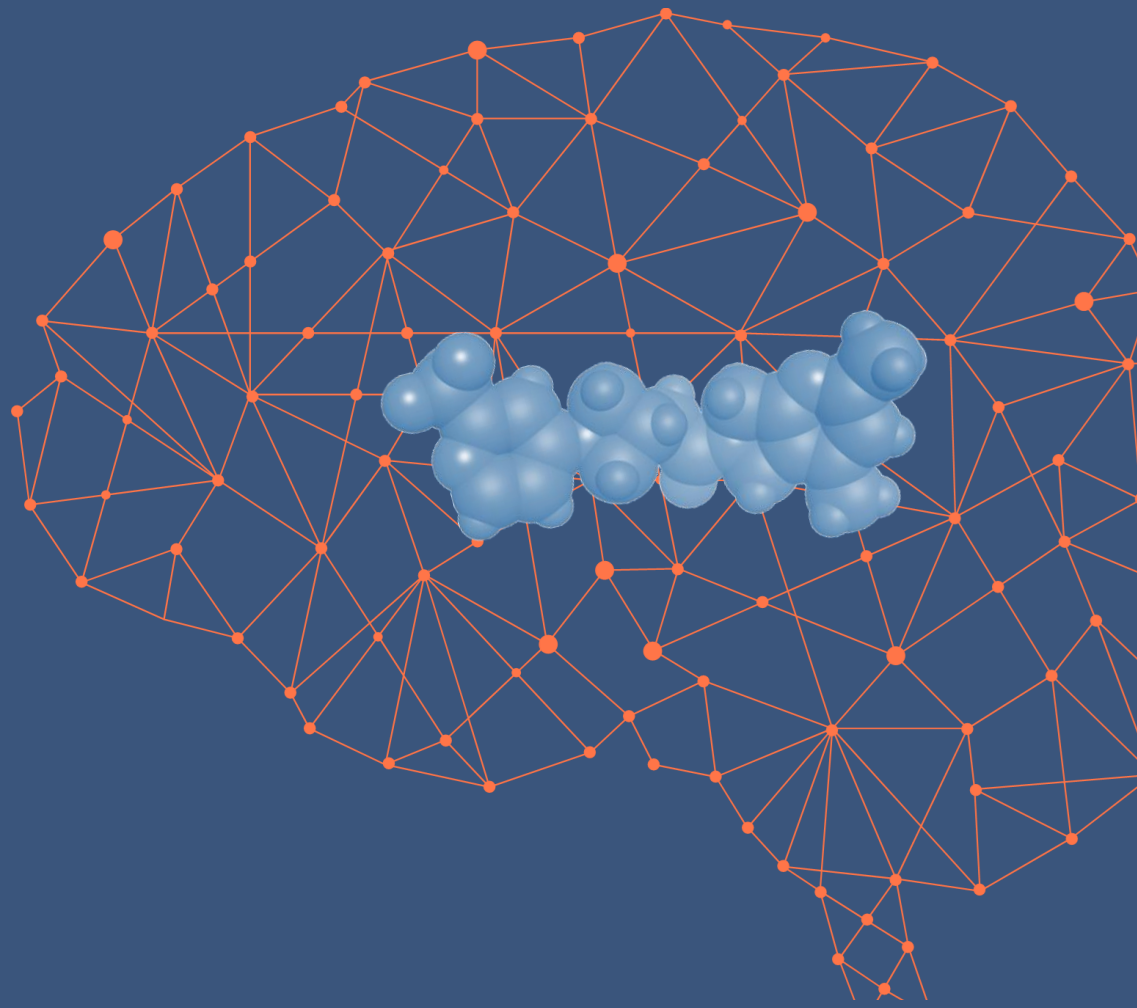
Combination with ARYA II – Key Highlights

- Provides a faster path to becoming a public company
  - Addresses one of the leading questions from potential crossover investors by enabling Cerevel to go public in one step vs. a typical two step process including crossover and IPO
  - Provides an investment structure for public investors to enable a potential business combination that appropriately capitalizes Cerevel while meaningfully reducing market risk
- Capitalizes Cerevel with an expected $445 million[1] raise through the reverse merger and PIPE to fund broad portfolio of neuroscience assets
  - Expected to provide cash runway for key catalysts into 2023, including:
    - Up to six data readouts across diversified pipeline of early and late stage programs
    - Additional IND filings for novel MOAs in new indications
- Price discovery streamlined and reduced execution risk in volatile markets
  - Satisfies investors' desire for larger capital raise to meet increased market demand
- Ability to establish premier shareholder base capable of supporting the company into the future
- Establish a broad syndicate of banks and research analysts that follow the stock post closing

(1) Projected cash balance including cash held in trust, expected cash on Cerevel's balance sheet, expected PIPE financing of $320 million, assuming no shareholder redemptions or warrant exercises and including transaction costs.

M4 PAM (CVL-231) in Schizophrenia

Additional Slides



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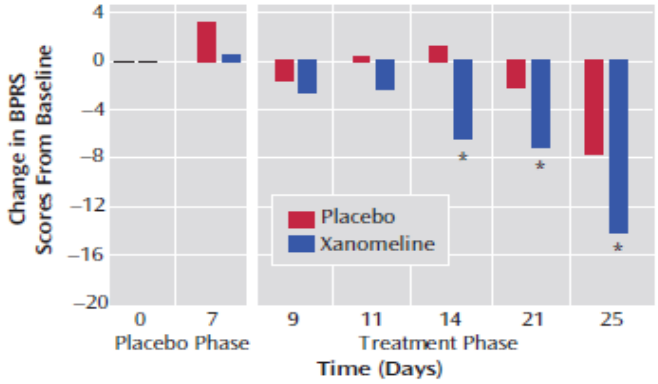
Xanomeline Clinical Data: Compelling Activity, Limited by Side Effect Profile

Xanomeline (Non-selective Agonist) Impacted Symptoms…

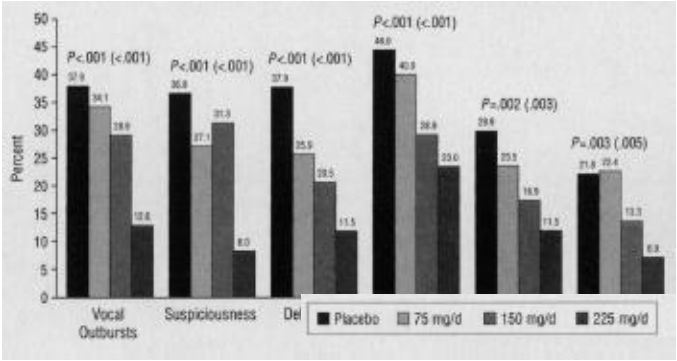
2008 Phase 2 in Schizophrenia

Statistically significant impact on total BPRS and PANSS scores in schizophrenia patients[1]



1997 Phase 2 in Alzheimer's Disease

Statistically significant impact on agitation and other psychosis-related endpoints in Alzheimer's patients[2]



…But Development Was Limited by GI Side Effects

Table 3. Adverse Events*

Event	Placebo (n=87)	Dose† Low (n=85)	Medium (n=83)	High (n=87)	Total (N=342)	P‡
Sweating	4 (4.6)	12 (14.1)	38 (45.8)	66 (75.9)	**120** (35.1)	<.001
Nausea	17 (19.5)	24 (28.2)	29 (34.9)	45 (51.7)	**115** (33.6)	<.001
Vomiting	8 (9.2)	11 (12.9)	33 (39.8)	37 (42.5)	**89** (26.0)	<.001
Dyspepsia	7 (8.0)	20 (23.5)	23 (27.7)	21 (24.1)	**71** (20.8)	.007
Chills	1 (1.1)	8 (9.4)	22 (26.5)	32 (36.8)	**63** (18.4)	<.001
Chest pain	1 (1.1)	5 (5.9)	13 (15.7)	10 (11.5)	**29** (8.5)	.004
Increased salivation	0 (0)	2 (2.4)	6 (7.2)	21 (24.1)	**29** (8.5)	<.001
Syncope	4 (4.6)	3 (3.5)	11 (13.3)	11 (12.6)	**29** (8.5)	.03
Fecal incontinence	0 (0)	4 (4.7)	1 (1.2)	6 (6.9)	**11** (3.2)	.04
Nausea and vomiting	2 (2.3)	0 (0)	1 (1.2)	7 (8.0)	**10** (2.9)	.009
Dysphagia	1 (1.1)	0 (0)	2 (2.4)	6 (6.9)	**9** (2.6)	.03

*Only events statistically significant at P<.05 are given. Values are number (percentage) of patients unless otherwise indicated.
†Low-dose group received 25 mg of xanomeline tartrate 3 times a day; medium, 50 mg 3 times a day; high, 75 mg 3 times a day.
‡Pearson χ^2 test.

Xanomeline's high rate of nausea, vomiting and dyspepsia is likely driven by non-selective muscarinic agonism

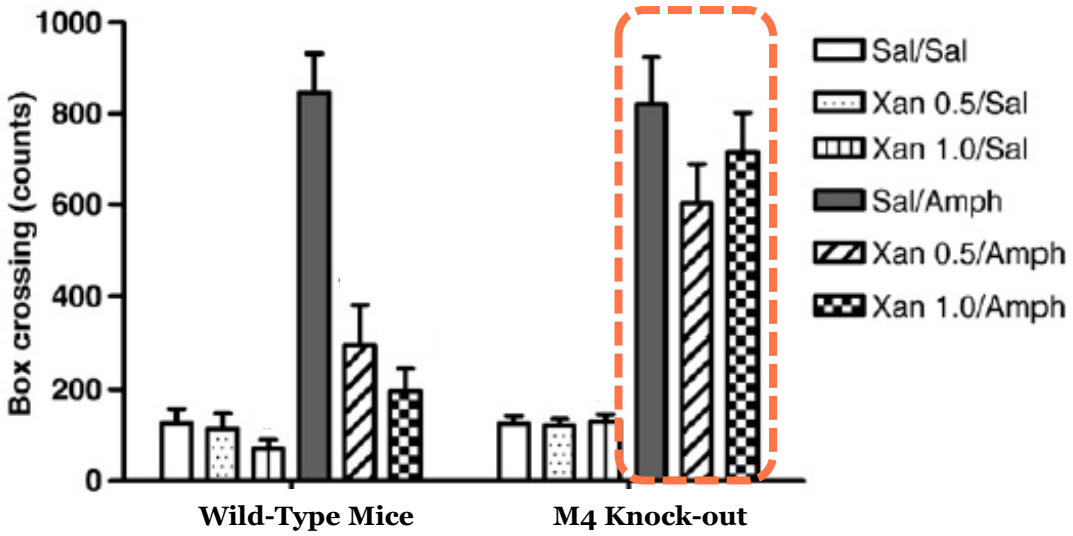
Mechanism Supported by Phase 2 Data for KarXT

- Karuna is developing a BID fixed-dose combination of xanomeline with trospium to offset side effects of GI, dry-mouth and constipation
- In a 5-week Phase 2 study, KarXT demonstrated an 11.6 point reduction in PANSS total score from baseline vs. placebo (p<0.0001)
- ~70 completers in each arm, with discontinuation rates similar between placebo and treatment group
- Represents a robust reproduction of 2008 xanomeline Phase 2 data in schizophrenia

Source: 1. Shekhar et al. Am J Psychiatry, Vol 165, Aug 2008. N=20. 2 active and 3 placebo-arm patients discontinued the study, none due to adverse events.
2. Bodick et al. Arch Neurol, Vol 54, Apr 1997. N = 343. 52% of patients in high-dose arm discontinued treatment due to adverse events.

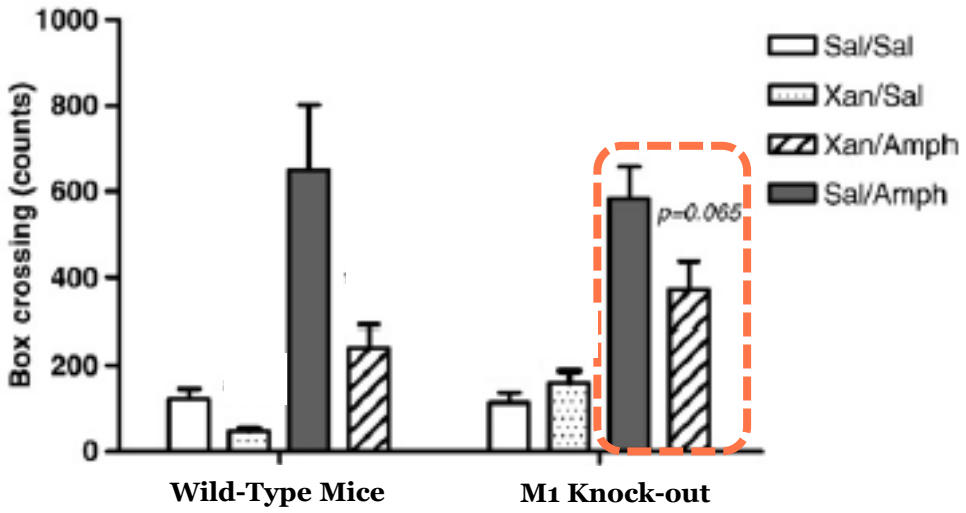
Preclinical Evidence: M4 Modulation Drives Antipsychosis

No Effect of Xanomeline in M4 Knock-out Mouse Model



Xanomeline had no effect on amphetamine-induced hyperactivity in M4 knock-out mice

Reduction in Hyperactivity in M1 Knock-out Mice



Xanomeline reduced hyperactivity in M1 knock-out mice

In mouse studies, M4 receptors drive the antipsychotic activity of xanomeline

Source: Woolley, et al. European Journal of Pharmacology 603 (2009)

Important Insights on Side Effects of M4 PAM

Results of a Phase 1 SAD trial indicated CVL-231 was generally well-tolerated with asymptomatic transient effects on heart rate and blood pressure

Phase 1 SAD Trial (N=17)

- Tested doses up to 30 mg
- Relatively well tolerated with no SAEs
- Most frequently reported treatment-emergent AEs: fatigue, dizziness, headache and dry mouth
- Moderate treatment-emergent transient increases in blood pressure and pulse rate observed
- Cardiovascular effects were asymptomatic and transient in nature

Insights

- Preclinical studies show CV effects attenuated with repeat dosing
- KarXT data also suggest that CV effects attenuate over time with repeat dosing
- Tolerability may be differentiated in schizophrenia patients and CV effects may be attenuated with repeat dosing and/or titration.

Phase 2 data for MK-7622 (M1 PAM) in Alzheimer's disease

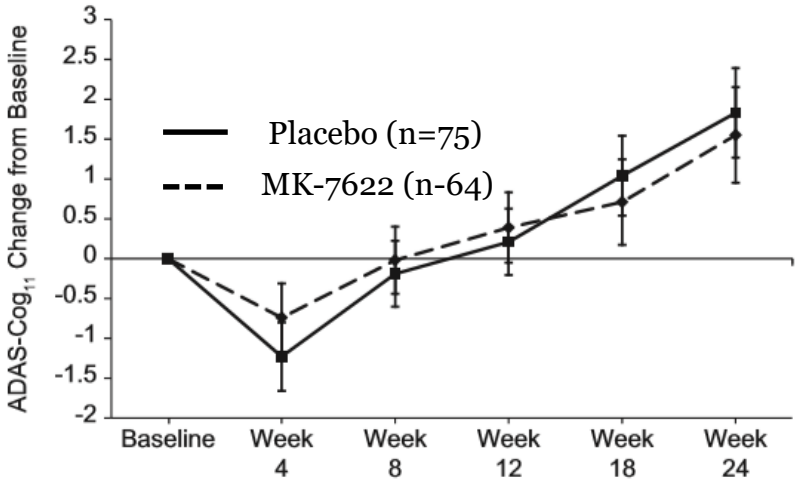
Summary

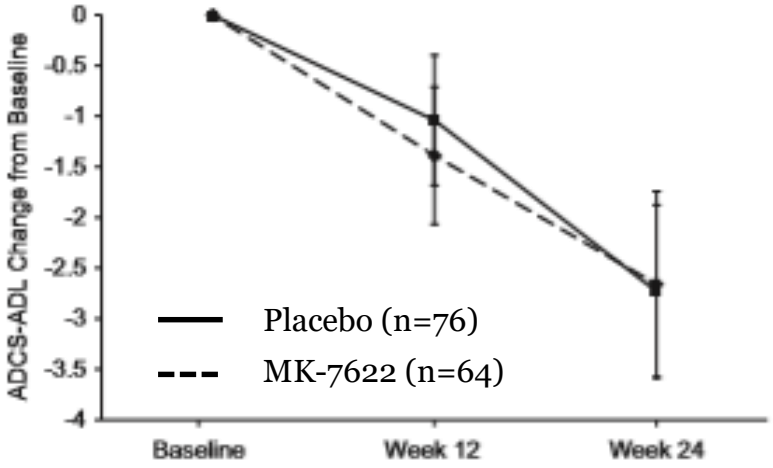
- Randomized double-blind proof-of-concept trial as adjunctive therapy in mild-to-moderate Alzheimer's disease
- Conducted by Merck; data published 2018
- Trial stopped early for futility

Results

- **No difference from placebo on either cognition or activities of daily living (ADL) scales**
- Discontinuation rate of 16% on MK-7622 vs 6% on placebo
- Cholinergically-related adverse event rate of 21% on drug vs 8% on placebo

Results in Cognition and ADL





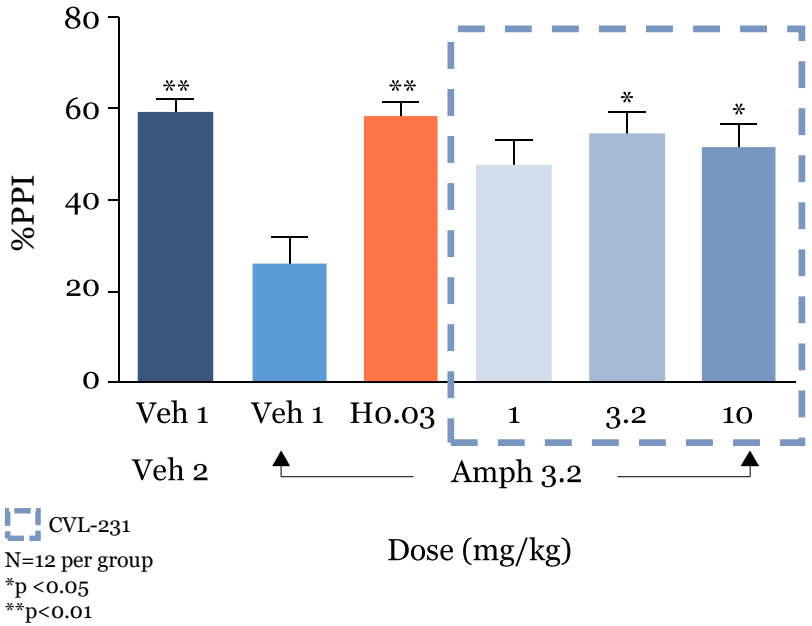
Side Effect Profile

Most Common AEs (>5%)	MK-7662 (n=119)	Placebo (n=120)
Diarrhea	18 (15.1%)	7 (5.8%)
Headache	11 (9.2%)	6 (5.0%)
Rhinorrhea	7 (5.9%)	1 (0.8%)
Urinary Incontinence	6 (5.0%)	0 (0.0%)
Weight Decrease	6 (5.0%)	2 (1.7%)
Urinary Tract Infection	6 (5.0%)	7 (5.8%)
Fall	2 (1.7%)	6 (5.0%)

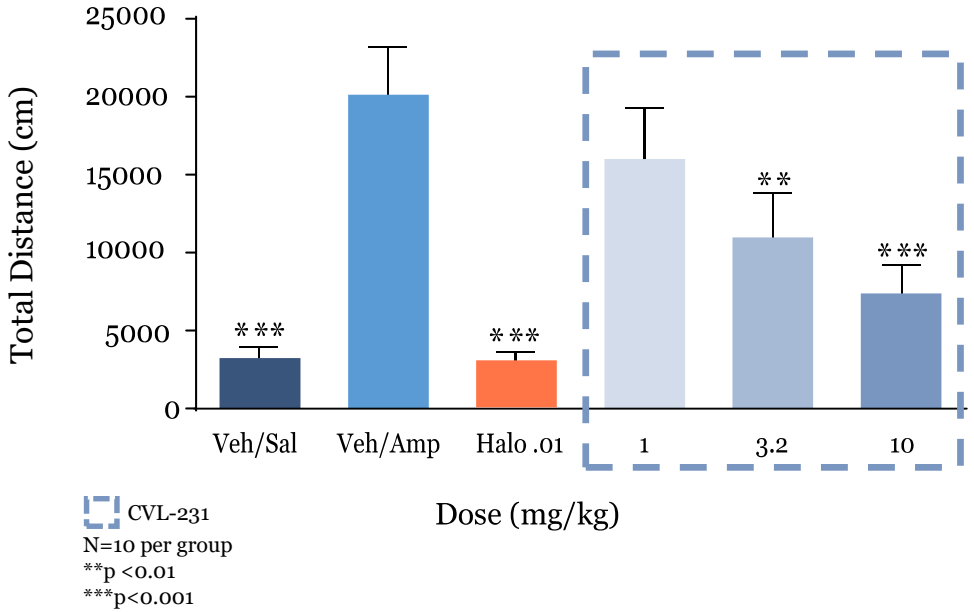
Source: T. Voss et al. / Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 173-18 1

M4 PAM Preclinical Data in Psychosis

CVL-231 showed similar effect to haloperidol in reversing amphetamine-disrupted Pre-pulse Inhibition (PPI) in rats



CVL-231 showed dose-dependent reductions on amphetamine-induced locomotion in rats



In multiple rodent models of psychosis, CVL-231 demonstrated antipsychotic activity consistent with xanomeline and atypical antipsychotics

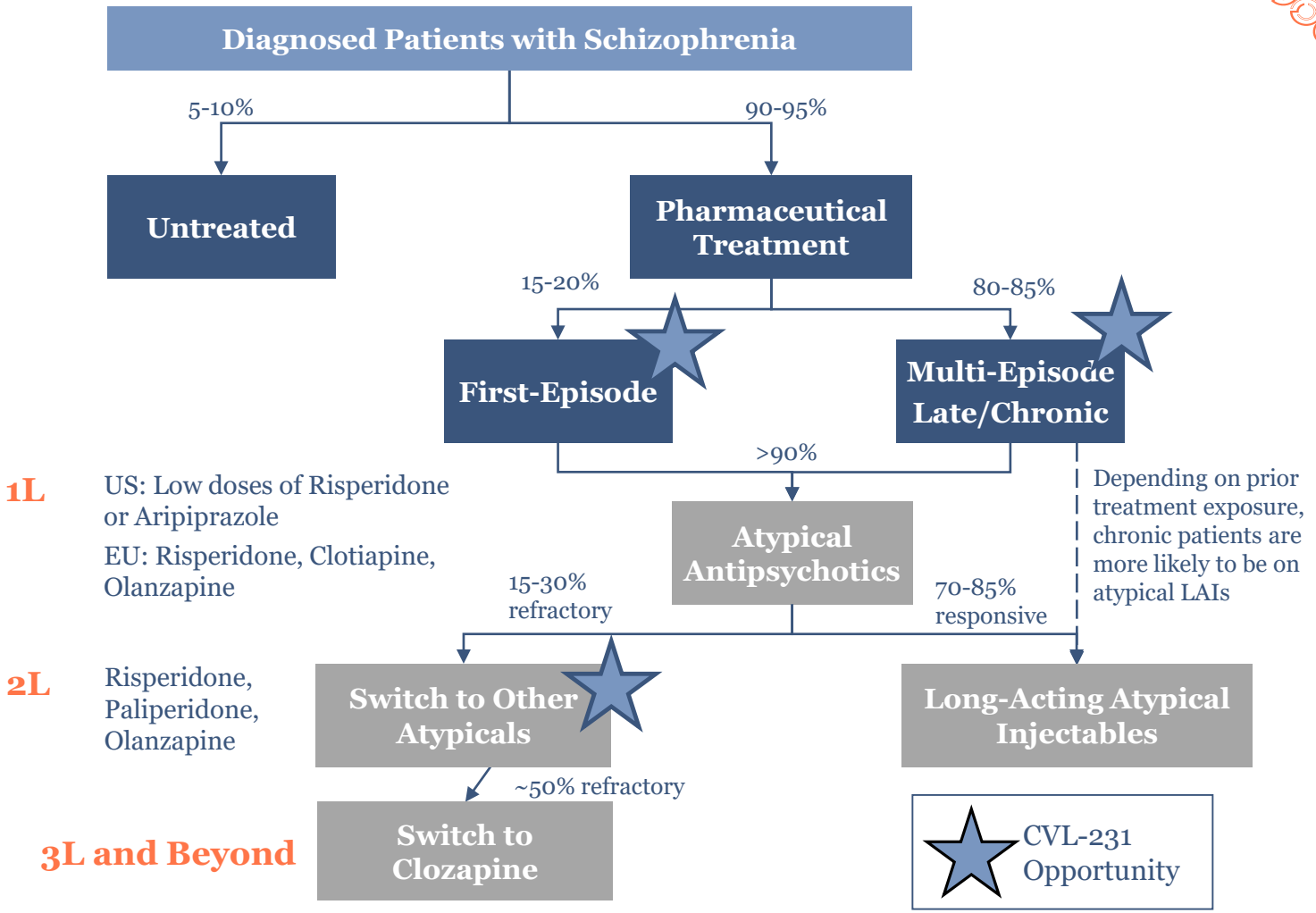
Source: Cerevel studies.

CVL-231 Commercial Potential in Schizophrenia

Potential for CVL-231 to be a New Standard of Care

- Potential for improved SE profile could position CVL-231 as first-line treatment of newly diagnosed and ongoing schizophrenia patients, including DRP
- If an improved tolerability and metabolic profile is demonstrated, CVL-231 could displace atypical antipsychotics in patients with treatment-related side effects

Multiple Potential Entry Points for CVL-231 in the Treatment Paradigm

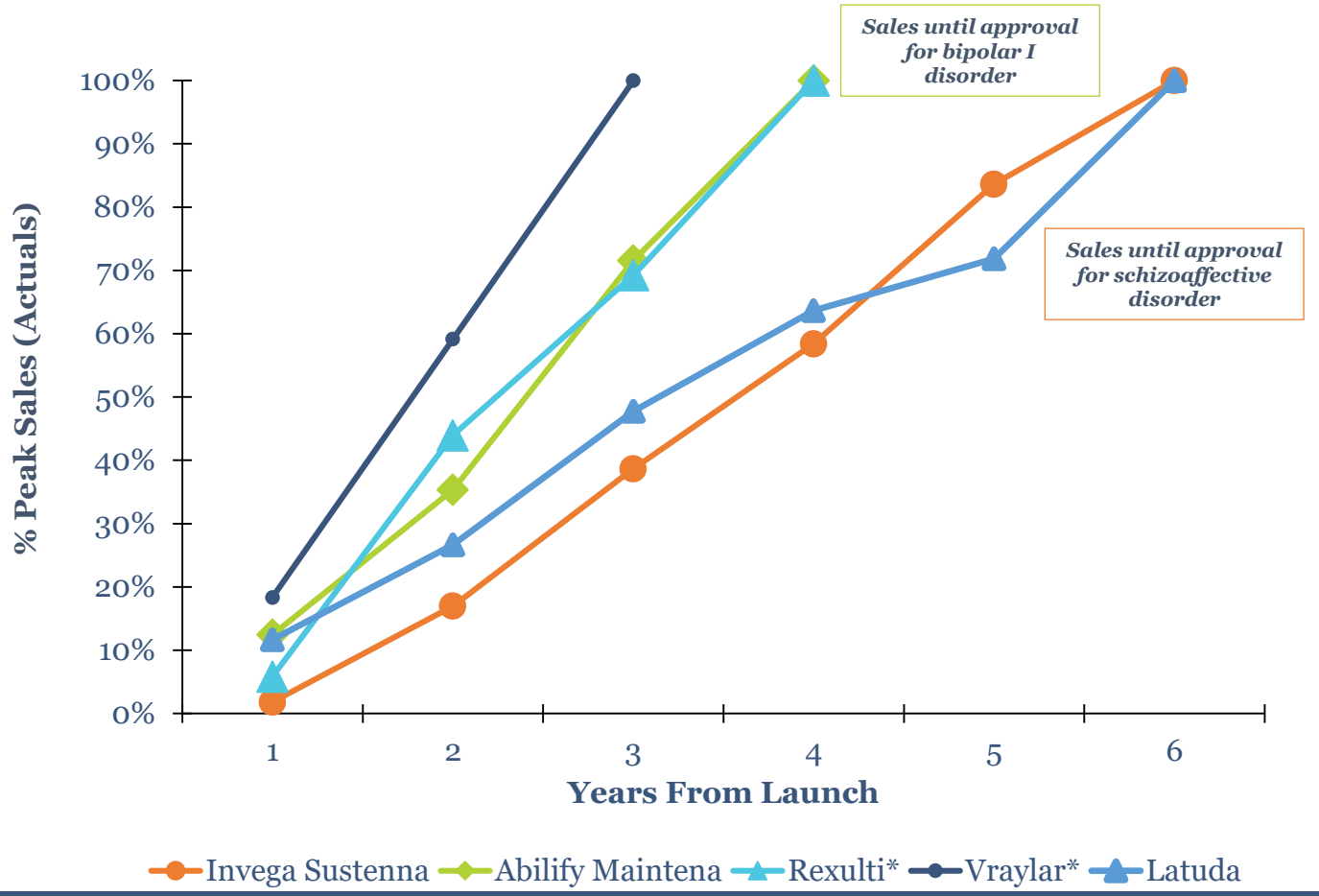


Schizophrenia Therapies: Rapid Historic Uptake Despite Limited Differentiation

Drug	US 2018 Schizophrenia Sales	2018 US Share
Latuda (lurasidone)	$973M	13.5%
Invega Sustenna (paliperidone LAI)	$981M	6.2%
Rexulti (brexpiprazole)	$449M	8.1%
Abilify Maintena (aripiprazole LAI)	$331M	2.1%
Vraylar (cariprazine)	$164M	2.6%

Schizophrenia US Sales Ramp – Actuals

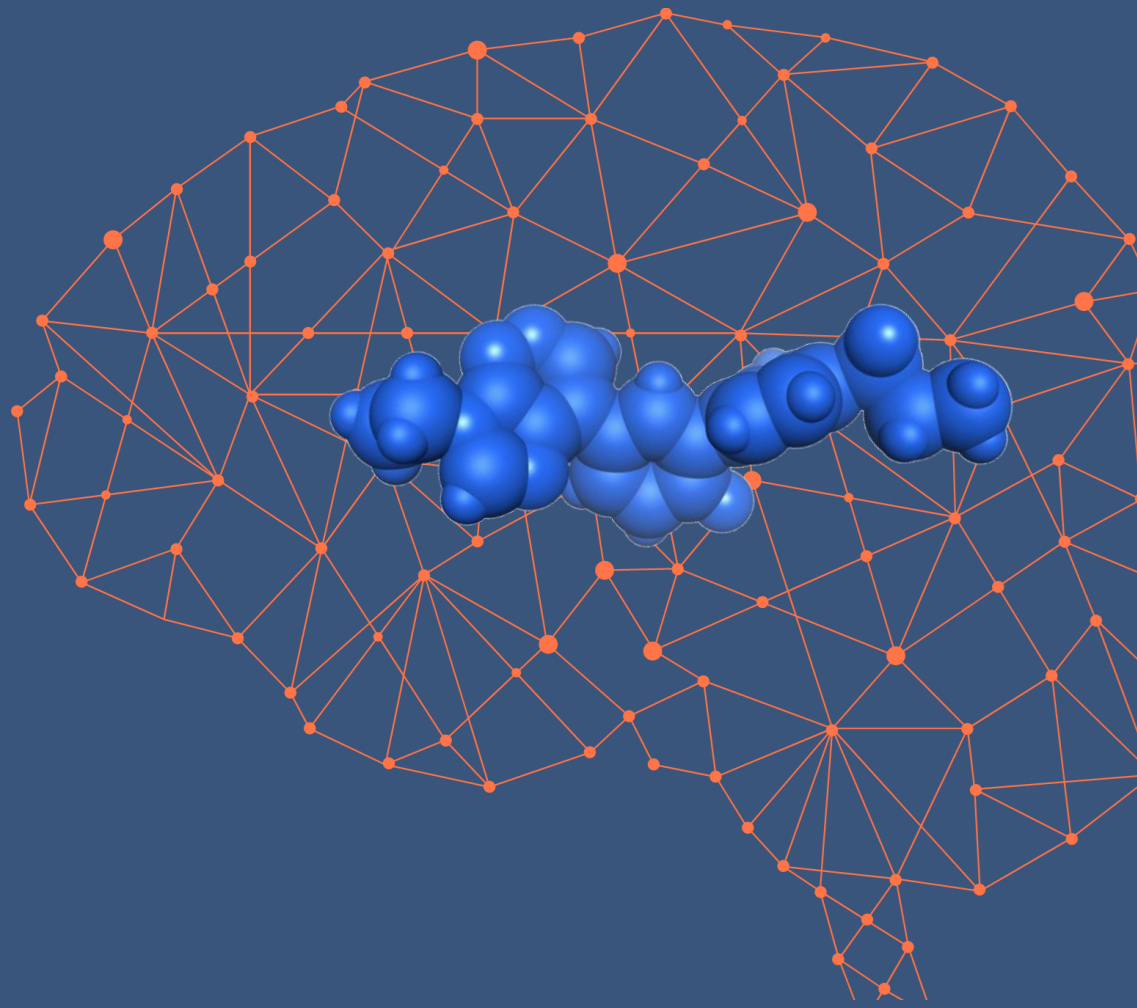
(through 2018 or until first non-schizophrenia indication launch)



Source: Huron analysis, EvaluatePharma.
*Represents sales until first non-schizophrenia indication launch.

GABA PAM (CVL-865) in Epilepsy

Additional Slides



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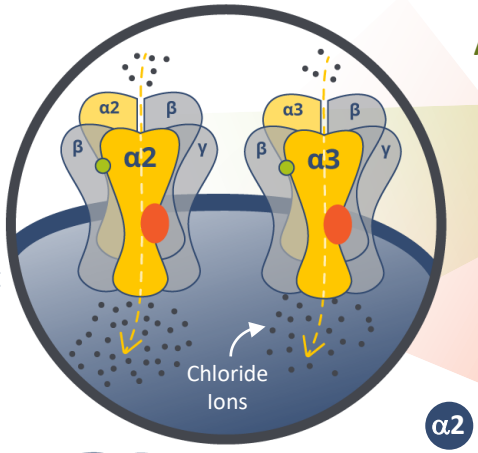
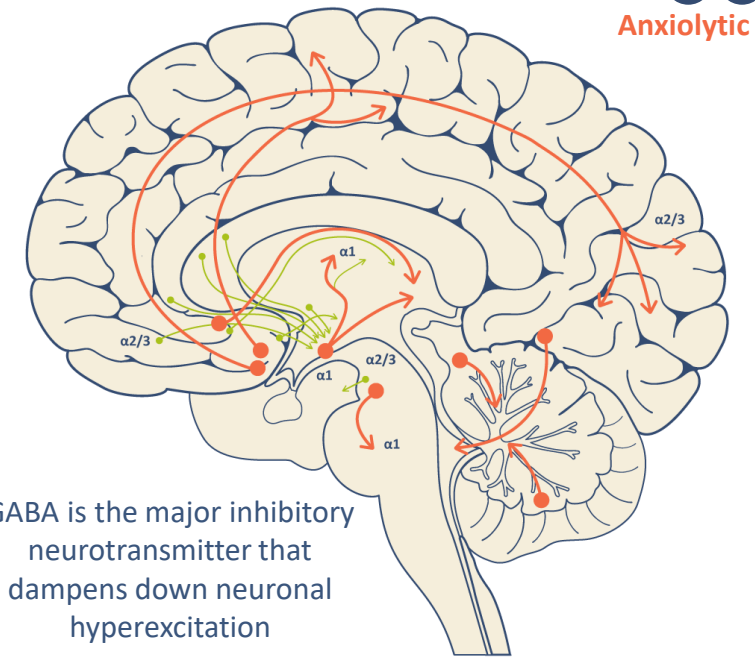
CVL-865 Mechanism: Selective α2/3/5 $GABA_A$ Receptor PAM

α2 α3 α5 CVL-865 is designed to selectively enhance $GABA_A$ receptor activity at α2/3/5 subunits

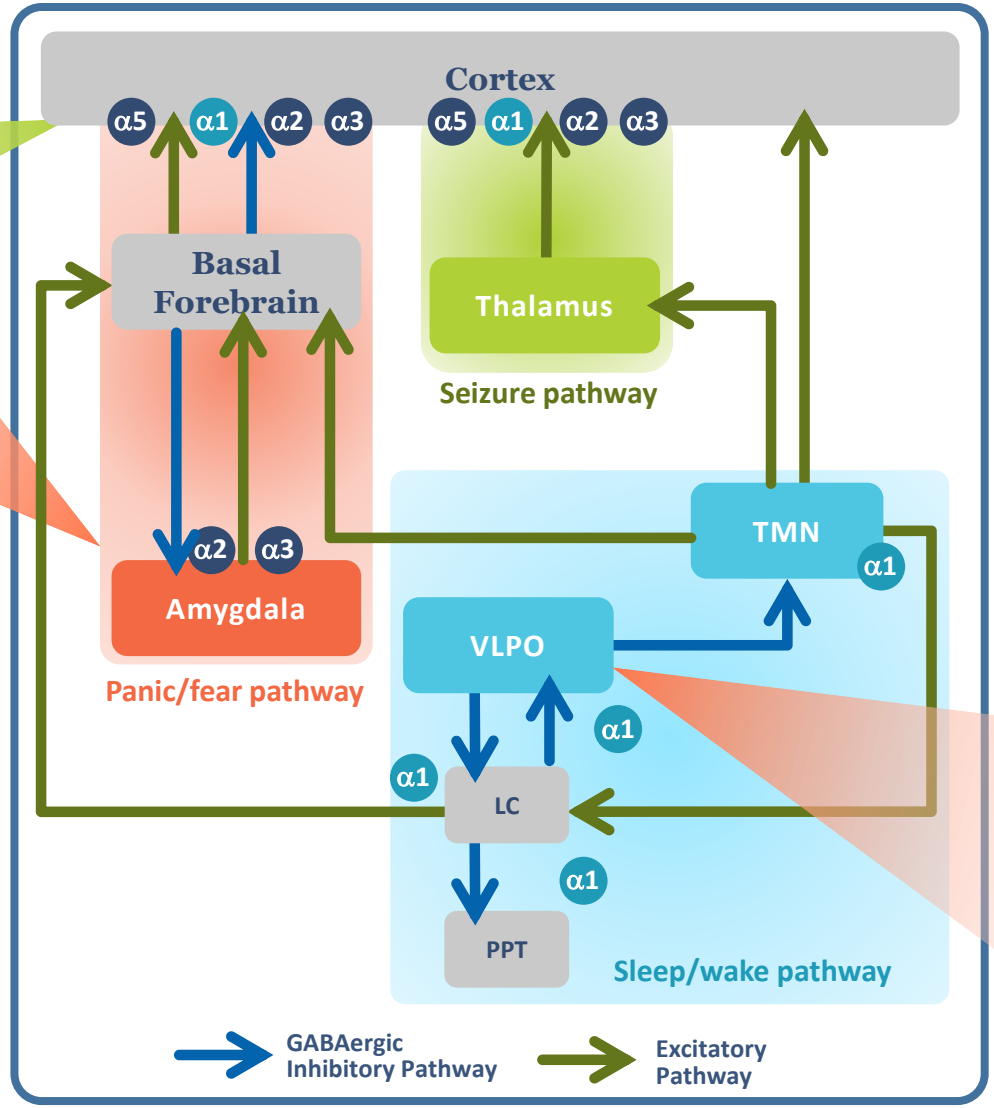


α1 α2 Anticonvulsant effect

α2 α3 Anxiolytic effect



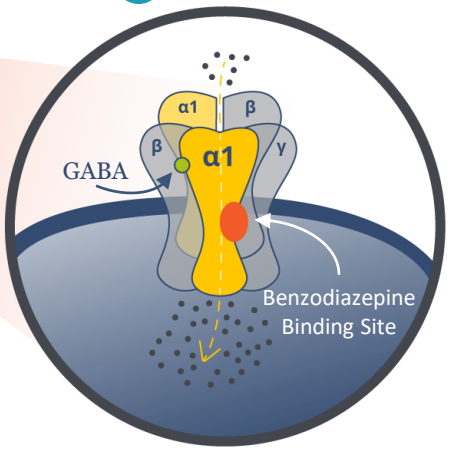
GABA is the major inhibitory neurotransmitter that dampens down neuronal hyperexcitation



α1 Benzodiazepines ***non-selectively*** enhance $GABA_A$ receptor activity, which can cause side effects primarily driven by α1 subunit activation

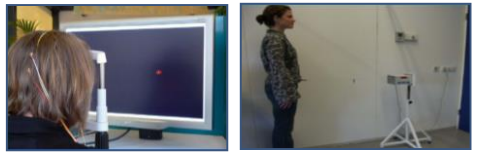
- Sedation
- Cognitive impairment
- Addiction

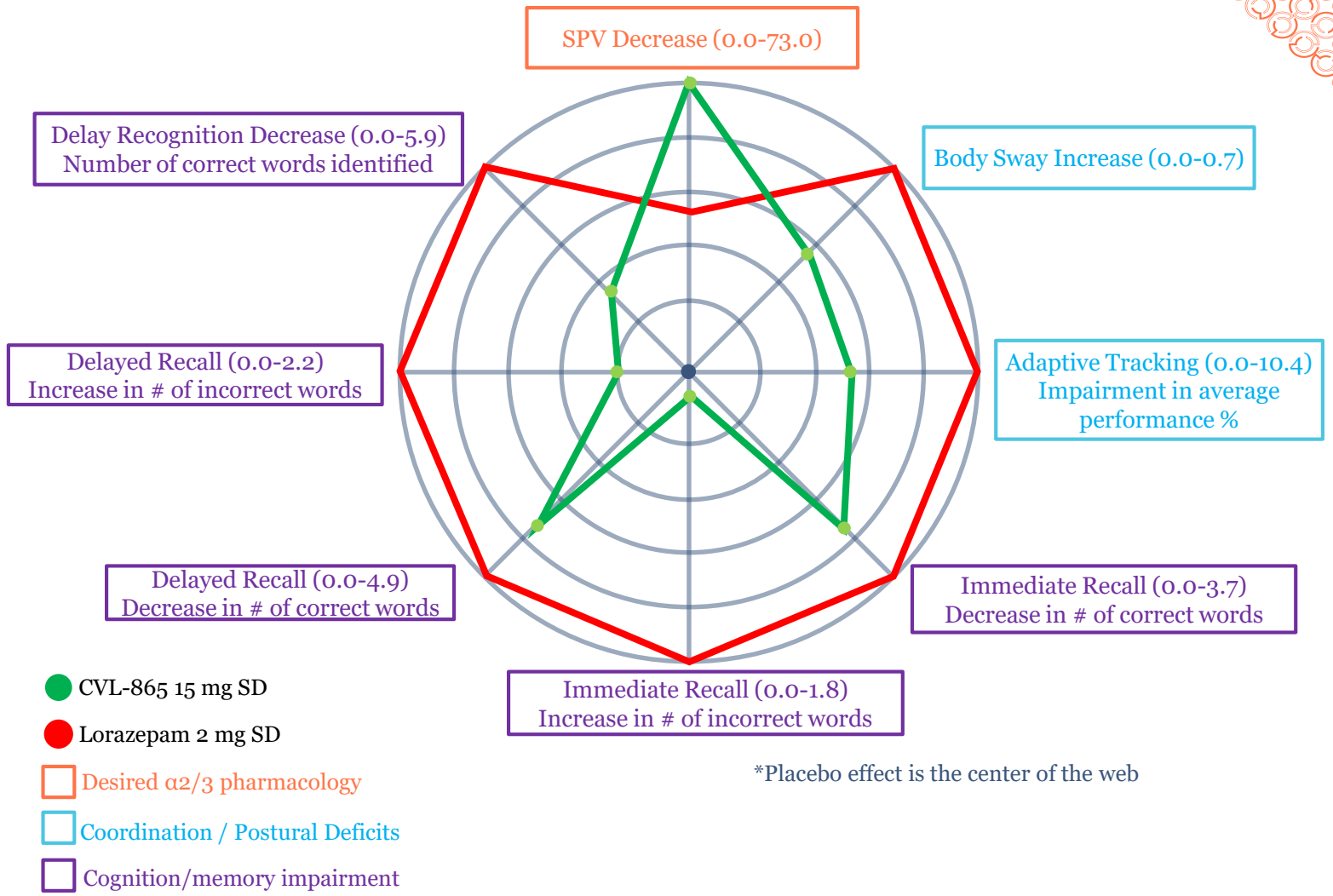
α1 Sedative effect



CVL-865: Favorable Pharmacology in NeuroCart, Differentiated From a BZD

- **NeuroCart is a comprehensive battery of tests to evaluate CNS functional domains**
- **CVL-865 first-in-human study tested the following brain functions based on known $GABA_A$ receptor pharmacology:**
  - Saccadic peak velocity (SPV) – desired α2/3 pharmacology (a decrease in SPV is viewed as an indicator of anti-seizure potential)
  - Body sway - undesired α1 pharmacology
  - Adaptive tracking - undesired α1 pharmacology
  - Visual-verbal learning test - undesired α1/5 pharmacology
  - Quantitative EEG – identify signature of α2/3 pharmacology
- Relative to 2 mg lorazepam, CVL-865 demonstrated a larger decrease in SPV and smaller impairment on body sway, adaptive tracking and cognitive tests





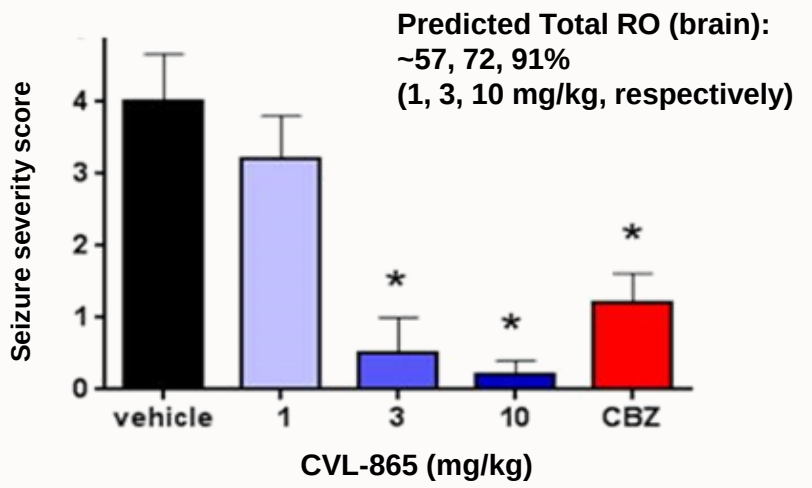
*Placebo effect is the center of the web

Source: IND B7431001 - Phase 1 double-blind, randomized, placebo controlled, cross-over single dose escalation study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of PF-06372865 in healthy subjects

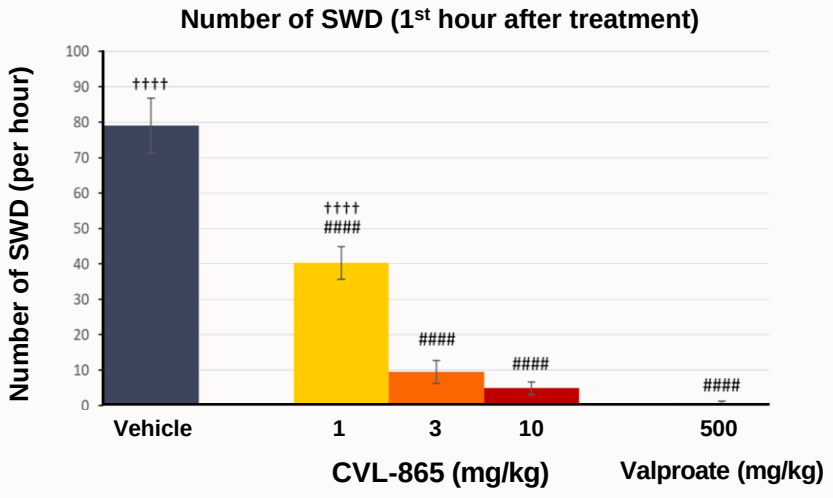
CVL-865 was Anticonvulsant in a Range of Preclinical Models

- Strong correlation of animal models of seizures translating to clinical activity across mechanism
- CVL-865 demonstrated broad spectrum of activity
  - Amygdala kindling is a validated model for predicting activity in focal seizures
  - Genetic absence epilepsy rat model predictive of activity in absence (generalized) seizures
  - CVL-865 also appeared active in pentylenetetrazol and pilocarpine-induced seizures

Amygdala Kindled Seizures in Rats: Focal Seizures



Genetic Absence Epilepsy in Rats: Generalized Seizures



CVL-865 demonstrated preclinical anticonvulsant activity, potentially through high receptor occupancy at α2 subunits

Duveau et al., CNS Neurosci Thr 2019; Owen et al., J Med Chem 2019

CVL-865 TPP: Benzo-like Activity for *Chronic* Treatment

CVL-865 Summary

- Large markets (Focal & Generalized)
- Novel mechanism
- Potential for better activity than chronic treatment alternatives
- Potentially favorable side effect profile
- Attractive pricing analogs

Pricing & Launch

- High branded sales despite many generics
- Branded US price analogs >$10K/year
- Complex to change treatment in epilepsy
- 7-year+ average uptake in the category

History of CVL-865 Development

Results of early clinical trials were believed to be limited by Pfizer's self-imposed dosing cap

Micronuclei formation observed in early preclinical rat studies

Pfizer self-imposes a dosing cap of 1/10 the NOAEL. Clinical trial doses limited to 7.5 mg BID.

2014:
Multiple Early Phase 1 studies

Safety / Tolerability up to 7.5 mg BID (15 mg single dose)

Early 2016:
Additional genotoxicity studies in rats

Feb 2017:
Completion of 7-patient Phase 2 Photoepilepsy trial

Single doses up to 52.5 mg

March 2017:
FDA Response to Type C meeting Request

Permits evaluation in multi-dose clinical trials of doses of up to 50 mg

2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019

2015: Phase 2 clinical trials in Generalized Anxiety Disorder and Chronic Low Back Pain

Doses limited to max of 7.5mg BID

Dec 2016: FDA Type C meeting Request Submitted

To discuss increasing maximum dose for future clinical trials

Feb 2018:
Completion of Phase 1 MAD Study

Doses up to 42.5 mg BID for 2 weeks

Early preclinical and clinical studies (subtherapeutic doses)

Clinical studies at expected therapeutic doses

Regulatory correspondence

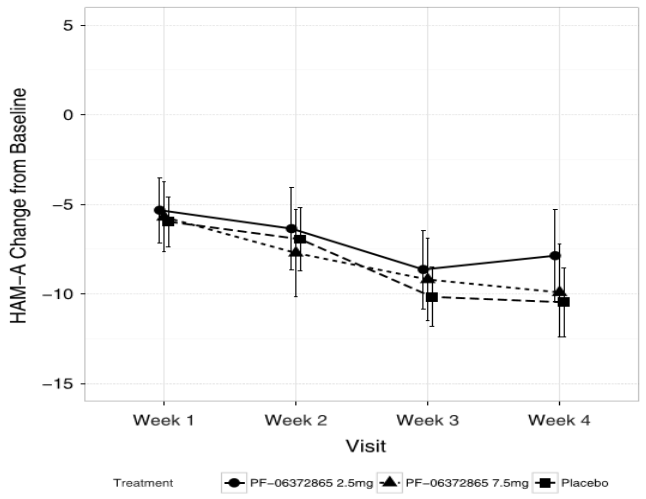
Prior Clinical Studies in Anxiety and Chronic Low Back Pain

Use of subtherapeutic doses and small sample size believed to account for lack of activity in prior trials

Phase 2: Generalized Anxiety Disorder

- Included drug-resistant patients on continued background treatment
- Sequential parallel comparison design
- Primary endpoint: HAM-A (minimum score at entry 20-22)
- 4 weeks on treatment: 2.5 mg BID CVL-865, 7.5 mg BID CVL-865, placebo
- Study stopped early for project prioritization - 90 enrolled of planned 384

CVL-865 not differentiated from placebo on HAM-A

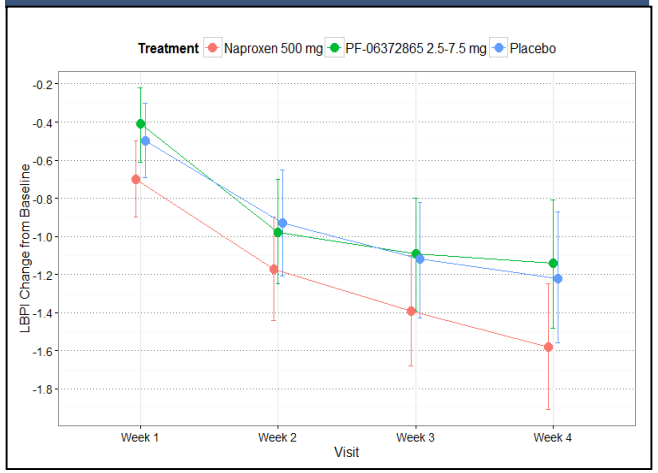


> 50% receptor occupancy remains unexplored in anxiety

Phase 2: Chronic Low Back Pain

- Included patients with > 6 months low back pain without radiculopathy
- Primary endpoint: change from baseline in low back pain score (measured on numerical rating scale)
- 4 weeks on parallel treatment: 7.5 mg BID CVL-865, placebo, 500 mg naproxen BID (positive control)
- Study stopped early for futility following a planned interim analysis after 50% subjects had completed treatment

CVL-865 not differentiated from placebo, naproxen



> 50% receptor occupancy remains unexplored in pain

CVL-865 Favorable Side Effect & Tolerability Profile Across Trials

CVL-865 has been tested in 289 subjects and was generally well-tolerated. There have been no clinically significant side effect observations from physical examination, vital sign measurements, laboratory safety assessments, or ECG parameters and no reports of sedation across single and multiple dose trials

I. Across Phase 1 trials:

- 81 healthy subjects received single doses of CVL-865 (0.04 to 100 mg); 55 healthy subjects received multiple doses of CVL-865 (2.5 to 42.5 mg BID)
- Most common AEs: dizziness, somnolence, and fatigue. All AEs across trials have been mild or moderate in severity
- No drug-related SAEs in Phase 1 trials
- Titration in multiple dose healthy volunteer studies appeared to reduce the incidence of somnolence and dizziness

II. Across Phase 2 trials:

- 146 subjects received multiple doses of CVL-865 (2.5 to 7.5 mg BID); 7 subjects with documented photosensitive epilepsy received single doses of 17.5 mg and 52.5 mg in a crossover trial
- Most common AEs: dizziness and somnolence; the majority of AEs were mild or moderate
- In Study B7431007, there was limited increase in sleepiness as measured by the Epworth Sleepiness Score with either CVL-865 7.5 mg, CVL-865 2.5 mg or placebo at Week 2 and Week 4
- In Study B7431006, one patient experienced an SAE (transient ischemic attack) that was considered related to CVL-865 by the investigator. The patient had a history of high cholesterol levels and high blood pressure and was diagnosed with diabetes mellitus after the onset of TIA
- Use of titration in multi-dose Phase 2 trials appeared to mitigate CNS effects, including somnolence, over time

III. Other considerations:

- No evidence to date of withdrawal effects
- No evidence of the bone marrow effects seen in preclinical studies
- Reproductive effects are being addressed for all trials with requirements for contraception and standard warnings

CVL-865: Phase 1 Program in Acute Anxiety

HYPERCAPNIA: PROOF-OF-PRINCIPLE MODEL FOR GABA (PAM) ANXIOLYTIC ACTIVITY

- CO_2 inhalation challenge (hypercapnia) well established in healthy volunteers and patients with panic disorder
- Purported MOA for anxiety induced by hypercapnia is decreased GABA and increased noradrenaline
  - Panic patients have fewer inhibitory $GABA_A$ receptors
- Model sensitive to drugs used to treat anxiety disorders (including BZDs) and emerging new treatments with novel mechanisms

KEY TRIAL DESIGN ASPECTS

Healthy volunteers

Primary endpoints: Panic symptoms list[1]

Two-way crossover design to reduce potential habituation effects of repeated CO2 exposure

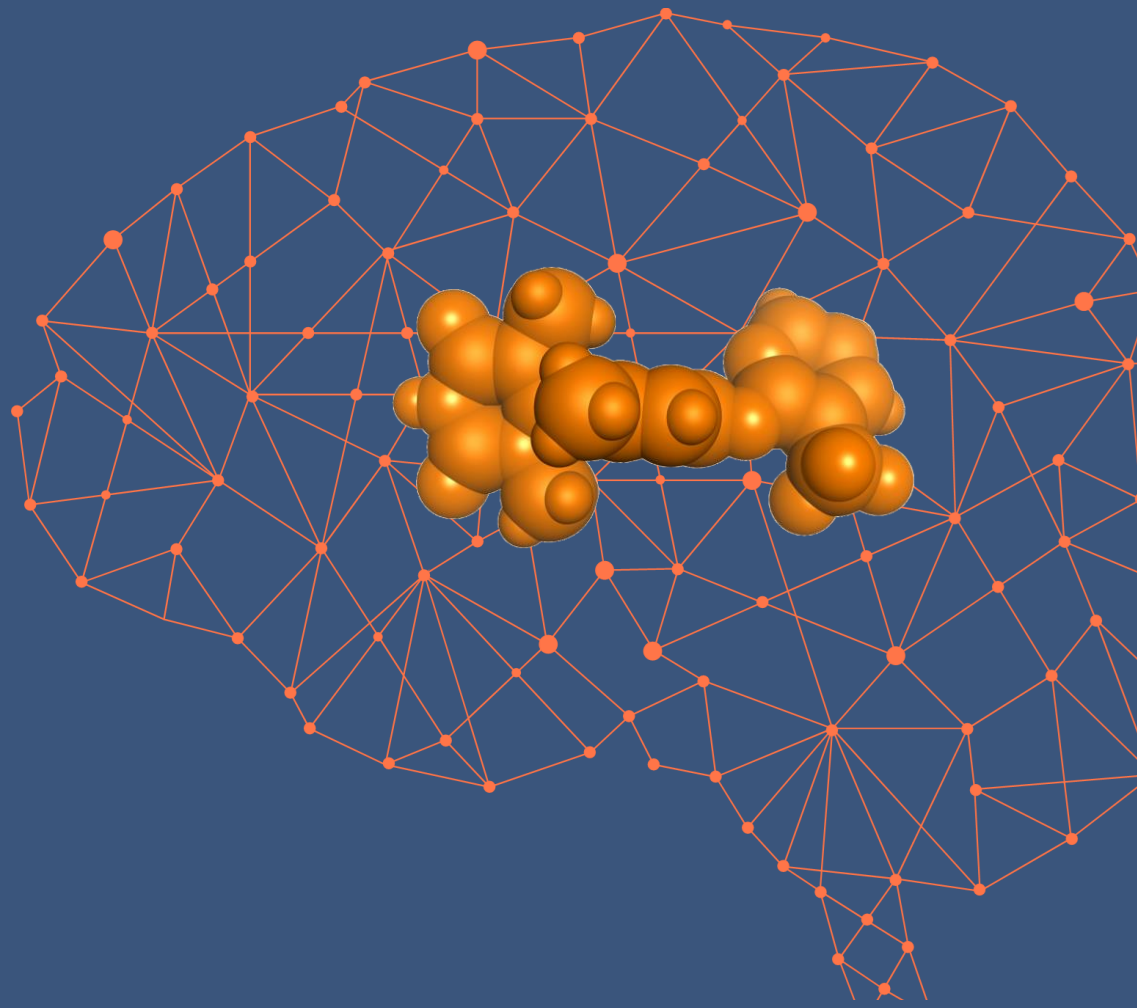
Multiple doses over 8 to assess "chronic" activity

Each cohort compared to placebo:
Cohort 1 (n=18) - 25 mg BID CVL-865 (~80% RO)
Cohort 2 (n=18) - 1 mg BID alprazolam (~15% RO)
Cohort 3 (n=18) - 7.5 mg BID CVL-865 (~60% RO)

1. **The Panic Symptom List (PSL)** includes 13 symptoms scored across a range of 0 (absent) to 4 (very intense) that is used to assess panic anxiety. Liebold et al. Trans Psychiatry. 2016.; Bailey et al. J Psychopharm. 2011.; Malizia et al. Arch Gen Psychiatry. 1998.; Salvatore et al. ASCP Poster 2019.
RO = Receptor Occupancy

Tavapadon in Parkinson's Disease

Additional Slides



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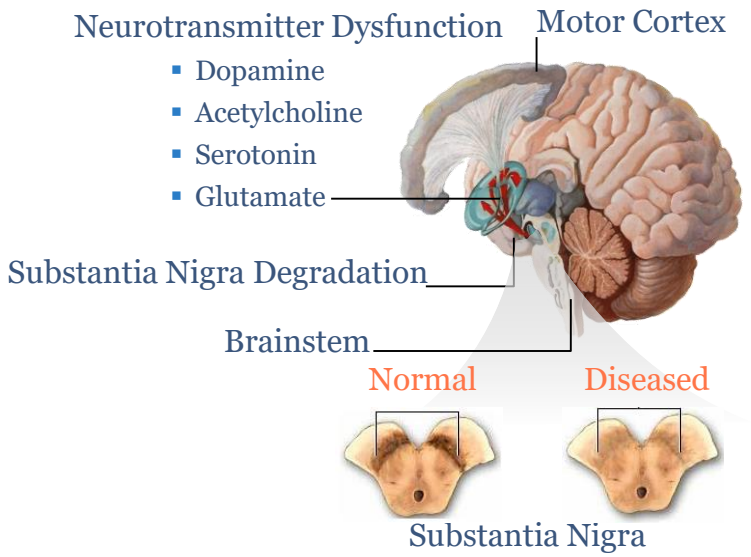
Parkinson's Disease Overview

Parkinson's disease is a progressive neurodegenerative disorder affecting regions of the brain that control balance and movement

Description

- Parkinson's disease is a degenerative neurological disorder characterized by progressive depletion of dopaminergic neurons in the substantia nigra region of the brain
- The lack of dopamine causes neurons to fire without normal control, leaving patients unable to control or direct their movement



Common Symptoms

- Symptoms of Parkinson's disease can be segmented into two categories – motor and non-motor:
  - Motor symptoms include tremor, decreased bodily movement (hypokinesia), slowness of movement (bradykinesia), stiffness and poor balance
  - Non-motor symptoms include cognitive dysfunction, psychosis, mood disorders, fatigue, *etc.*

Progression

- As symptom severity increases, patients often require increased doses of medication with decreasing efficiency, leading to "off" episodes
  - "Off" episodes are characterized by decreased motor function when patient's plasma drug levels fall below therapeutic levels
- Long-term levodopa use also leads to the development of dyskinesia or uncontrolled movement in PD patients

Genetic Indications

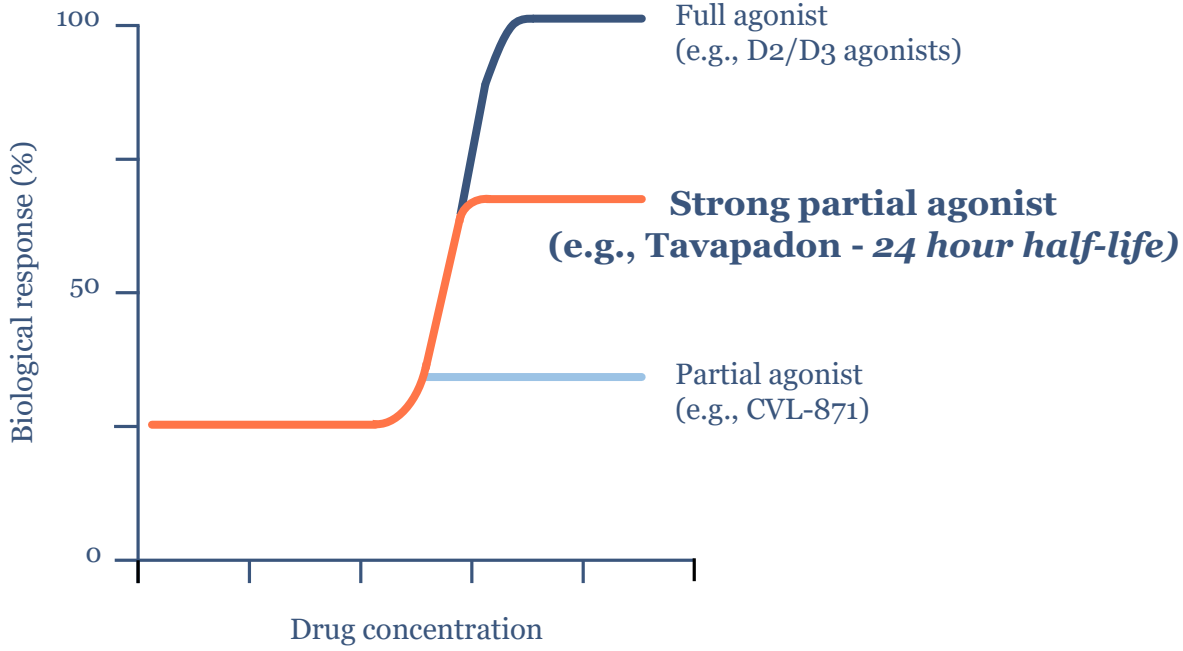
- Approximately 15% of Parkinson's patients have a family history of the disease. Such familial cases of the disease can be caused by mutations in the LRRK2, SNCA, PARK7, PINK1 or PRKN genes
- LRRK2 mutations attract greater attention from researchers since there are more known populations with this risk factor
  - G2019S is the most common LRRK2 mutation accounting for 3-6% of familial PD, and 1-2% of sporadic cases worldwide
  - This mutation is especially frequent in the Ashkenazi Jew and ArabBerber populations

Selectively Targeting Partial Agonism Designed to Improve Motor Control and Tolerability

D1/D5 Receptor Selectivity

D2/D3 Activation *(Indirect Pathway)*	Potential Effect	D1/D5 Activation *(Direct Pathway)*
+	Motor Control	++
	Cognition	++
	Motivation / Drive	++
-	Dose-Limiting Hypotension	
-	Impulse Control Disorders	
-	Sudden Daytime Sleepiness	

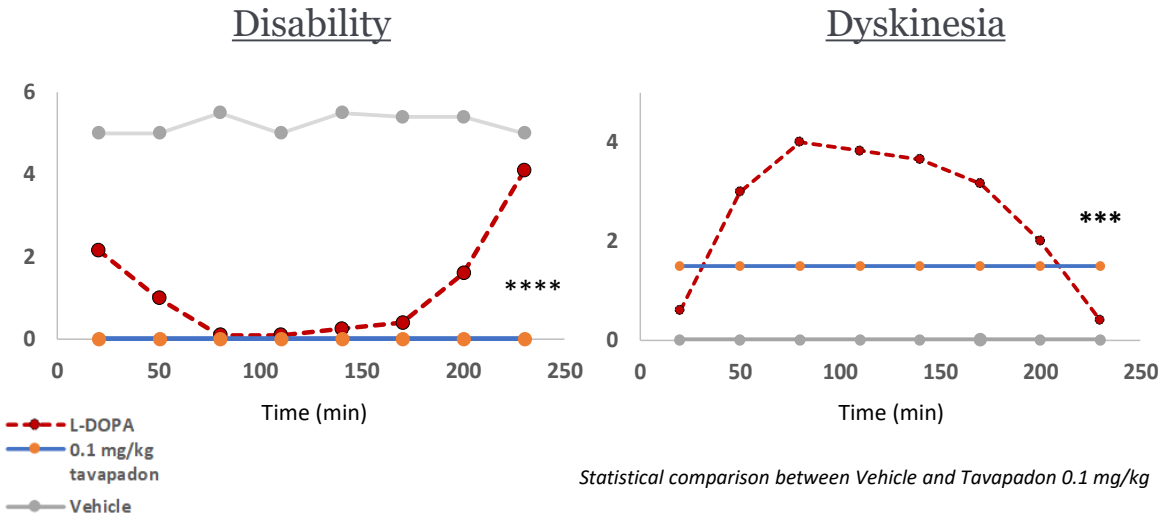
Degrees of Agonism



First ***Partial Agonist*** for Parkinson's ➔ Avoids Dyskinesias

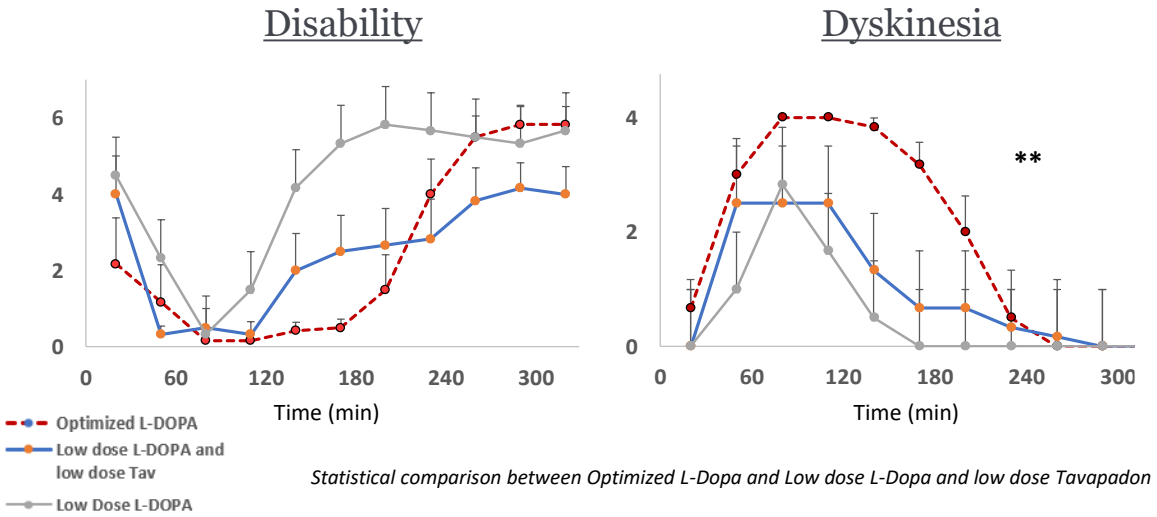
Unique and attractive combination of activity and low dyskinesias in highly translatable model of Parkinson's

Effect of Tavapadon vs. L-dopa on Disability and Dyskinesia



Statistical comparison between Vehicle and Tavapadon 0.1 mg/kg

Potential to Reduce L-dopa Dose to Achieve Motor Control with Reduced Dyskinesia



Statistical comparison between Optimized L-Dopa and Low dose L-Dopa and low dose Tavapadon

Compared to L-dopa, tavapadon robustly reduced parkinsonian symptoms in the MPTP-lesioned primate model with a more ***durable effect*** and ***lower dyskinesia*** levels

The combination of 33% L-dopa dose with 40% tavapadon dose showed ***similar activity to L-dopa alone with statistically significant reduction in dyskinesia***

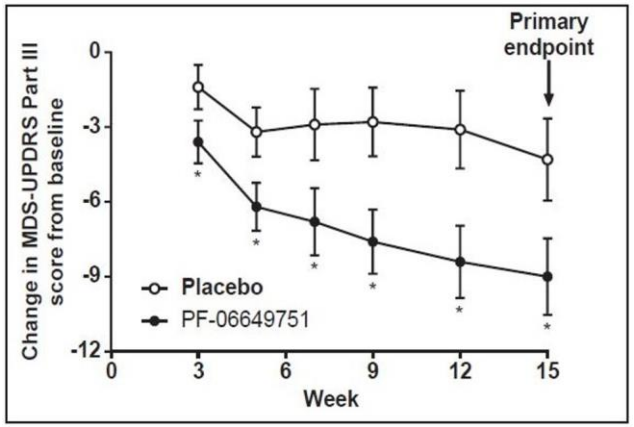
NHP = non-human primate. Mean Disability Score and Dyskinesia scores. Low-dose L-dopa at 33% of optimized L-dopa dose and low dose tavapadon at 0.04mg/kg.
Source: Young et al, ACS Chem. Neurosci., 2020.

Phase 3 Program Designed to Show Superior Treatment Profile

Phase 2 Results Inform Phase 3 Design

Phase 2 Results

MDS-UPDRS III



MDS-UPDRS II+III

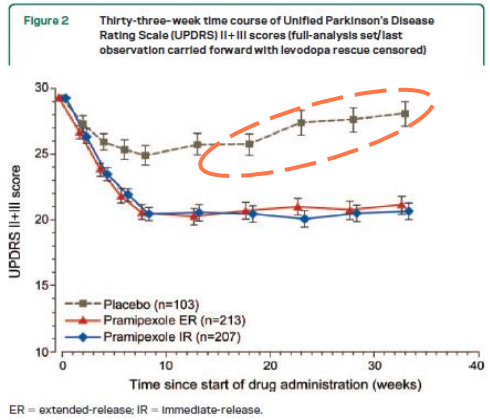
5.8 point improvement vs. placebo at week 15 on MDS-UPDRS II + III

Phase 3 Design

Baseline score of 2 or greater on MDS-UPDRS II

~2 point improvement vs. placebo on Part II, excluding participants with baseline score of 0 or 1 in Phase 2*

Placebo Attenuation at 6 Months



Further upside from forced titration to achieve maximum tolerated dose of tavapadon (less than 40% of patients were on the top dose in Phase 2)

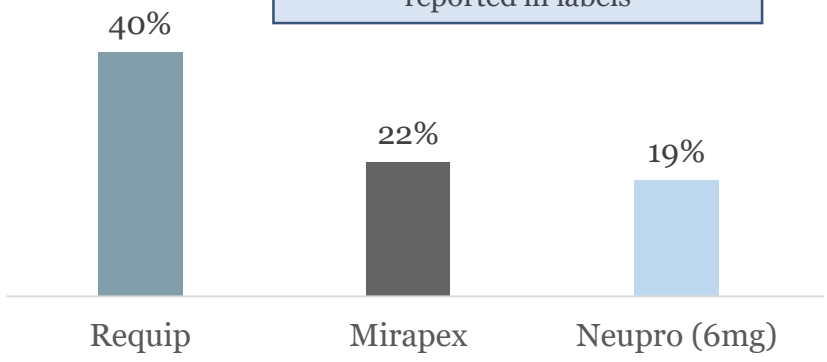
* Based on informal post hoc analysis

Historical D2/D3 Labels Show Significant Side Effect Profile

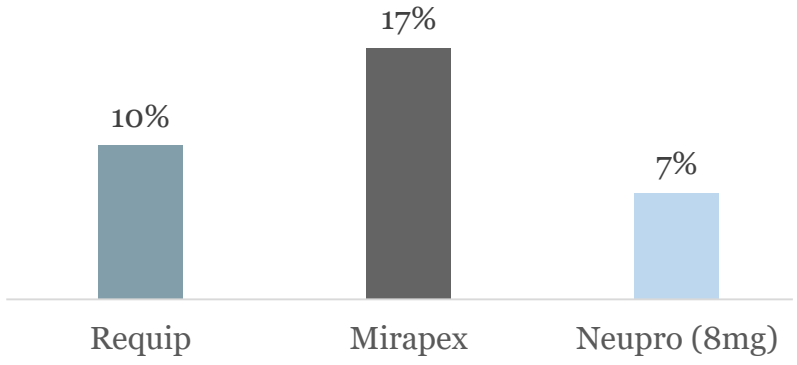
D2/D3 Side Effects: Sudden daytime somnolence, hallucinations, nausea and acute orthostasis

Somnolence
(Monotherapy)

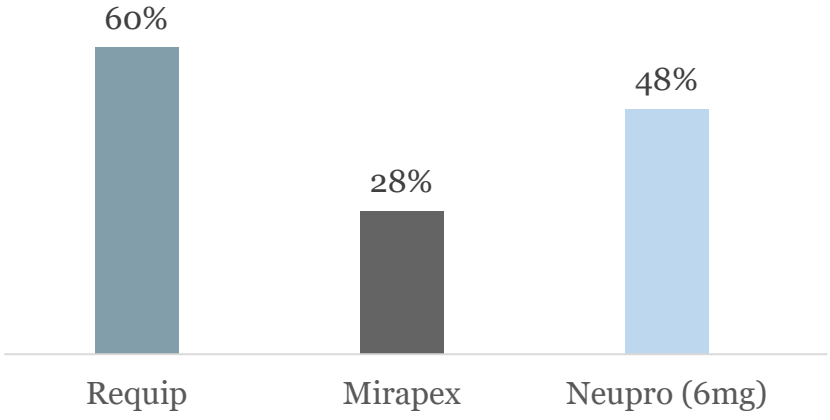
Sudden daytime somnolence is safety concern, but rates are not reported in labels



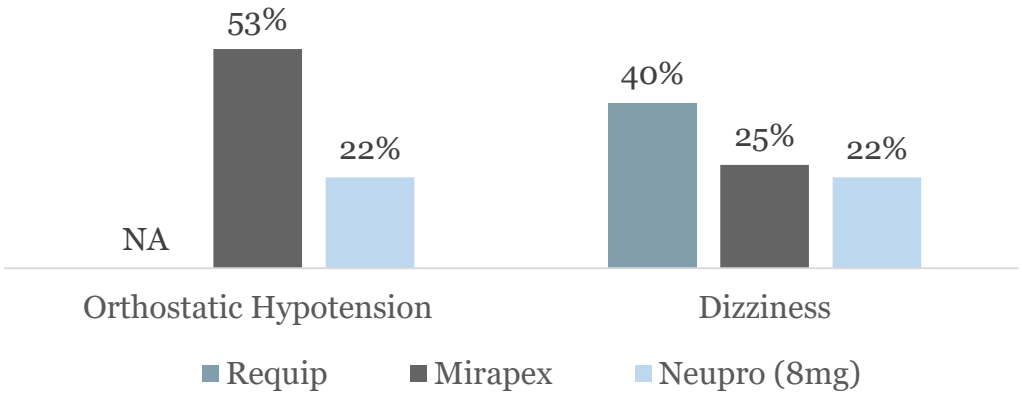
Hallucinations
(Adjunct to L-Dopa)



Nausea
(Monotherapy)



Hypotension-related Events
(Adjunct to L-Dopa)



Source: Requip, Mirapex, and Neupro labels (package inserts). Neupro 6mg dose indicated for early-stage PD; 8mg dose indicated for late-stage PD.
NA = Not reported in label (package insert).

Overview of Tavapadon Clinical Trials To Date

Protocol ID	Phase	Trial End Date	N= (active/total)	Design
B7601001	Phase 1	7 Feb 2014	18/18	Single ascending dose (0.25-2.5 mg) in healthy volunteers (HV)
B7601002	Phase 1	16 Apr 2015	61/77	Multiple ascending dose study in HV (0.5-5 mg QD)
B7601007	Phase 1	04 Dec 2014	9/9	Single ascending dose (0.25 and 0.75 mg) with an antiemetic
B7601006	Phase 1	14 Sept 2017	11/11	CYP3A Victim DDI
B7601005	Phase 1b	10 Mar 2016	45/50	Open label multiple ascending dose (5/15/25 mg) in PD patients Adjunct with lowering of levodopa dose
B7601009	Phase 1b	28 Feb 2016	18/18	Placebo controlled single ascending dose (0.75/1/3/6/9 mg) in PD patients Monotherapy
B7601003	Phase 2	10 Nov 2017	85/108	Adjunct with levodopa (1/3/7/15 mg) in advanced PD patients (w/ OFF-time ≥2.5h at baseline) Three week dose titration, 15 weeks total dosing
B7601011	Phase 2	29 Jan 2018	29/57	Monotherapy in newly diagnosed PD patients; flexible dosing Seven week dose titration, 15 weeks total dosing

Note: B7601017 OLE also enrolled 5 patients for 4 months with minimal data collected.

Thank you

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