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Investor Call: Alto Neuroscience Expands Precision Psychiatry Pipeline

NYSE: ANRO — June 3, 2025

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This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding the progress and timing of the clinical development of the programs across our portfolio, including the expected therapeutic benefits of our programs, and potential efficacy and tolerability thereof; the timing and nature of clinical data updates and milestones across our pipeline; the reproducibility of positive clinical data seen in prior trials of CTC-501/ALTO-207; our clinical and regulatory development plans for ALTO-207; expectations regarding our pipeline, operating plan, use of capital, expenses and other financial results; our cash runway projection; the competitive landscape and potential market opportunities for our product candidates; our ability to successfully establish or maintain collaborations or strategic relationships for our product candidates; expectations regarding current and future interactions with the U.S. Food and Drug Administration (FDA); the capabilities and development of our biomarker platform; our plans to develop, manufacture and commercialize our current product candidates and any future product candidates; and the implementation of our business model and strategic plans for our business, current product candidates and any future product candidates. The words “may,” “might,” “will,” “could,” “would,” “should,” “plan,” “anticipate,” “intend,” “believe,” “expect,” “estimate,” “seek,” “predict,” “future,” “project,” “potential,” “continue,” “target” and similar words or expressions, or the negative thereof, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks associated with: the impact of global economic uncertainty, geopolitical instability, or public health epidemics or outbreaks of an infectious disease on countries or regions in which we have operations or do business, as well as on the timing and anticipated results of our clinical trials, strategy, future operations and profitability; the delay of any current or planned clinical trials or the development of our drug candidates; the risk that the preliminary results of our preclinical studies or clinical trials may not be predictive of future or final results in connection with future clinical trials of our product candidates; our ability to successfully demonstrate the safety and efficacy of our drug candidates; the timing and outcome of interactions with regulatory authorities; and risks associated with obtaining, maintaining and protecting our intellectual property. These and other risks, uncertainties and important factors are described in the section entitled "Risk Factors" in our most recent Form 10-K and Form 10-Q filed with the Securities and Exchange Commission. Any forward-looking statements represent our views only as of the date of this presentation and we undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, the occurrence of certain events or otherwise. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements.

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Today’s speakers

Alto executive management team



Amit Etkin, MD PhD
Chief Executive Officer



Nick Smith
Chief Financial Officer and Chief Business Officer

External expert perspective



Michael Browning DPhil, MB.BS, MRCP, MRCPsych
Professor of Computational Psychiatry, University of Oxford



Alan Schatzberg, MD
Professor of Psychiatry and Behavioral Sciences, Stanford University

Today's agenda

- **Introduction** – Amit Etkin, MD, PhD – Founder & CEO
- **Dopamine biomarker insights** – Amit Etkin, MD, PhD – Founder & CEO
- **ALTO-207 opportunity and pramipexole data** – Amit Etkin, MD, PhD – Founder & CEO
  - **Pramipexole PAX-D Results –** Michael Browning DPhil, MB.BS, MRCP, MRCPsych – Professor of Computational Psychiatry, University of Oxford and PI of the PAX-D study
- **ALTO-207 clinical development** – Amit Etkin, MD, PhD – Founder & CEO
- **Expert perspective** – Alan Schatzberg, MD - Kenneth T. Norris, Jr. Professor of Psychiatry and Behavioral Sciences, Stanford University
- **Strategic & commercial case for ALTO-207–** Nick Smith – Chief Financial Officer
- **Q&A**



Precision Medicine for the Brain is Here.

OUR MISSION

Redefining psychiatry by leveraging individuals' neurobiology to develop personalized and highly effective medicines, helping patients get better faster.

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Acquisition of novel, patent-protected, dopamine agonist product candidates bolsters Alto's clinical-stage neuropsychiatry pipeline

Asset Overview

- **CTC-501/ALTO-207:** novel combination of pramipexole (dopamine D3/D2 agonist) and ondansetron (5-HT3 antagonist)
  - In development for treatment resistant depression (TRD)
- **CTC-413/ALTO-208:** novel combination of pramipexole and aprepitant (NK-1 inhibitor)
  - In development for Parkinson's disease (PD)

Both product candidates have completed successful Phase 2 trials

Strategic Fit

- Motivated by proprietary insights on dopamine biomarker in depression
- Strong existing clinical evidence combined with biomarker approach drives Alto's confidence in the clinical programs
- Adds late-stage, potentially pivotal*, clinical readout within current cash runway
- Complements existing pipeline programs in neuropsychiatry

Transaction Highlights

- **Upfront:** $1.75 M
- **Milestones:** total up to $71.5 M
  - Development: $18 M
  - Regulatory: $12.5 M
  - Commercial: $41 M

Deal structured to mitigate near-term cash impact and clinical development risk

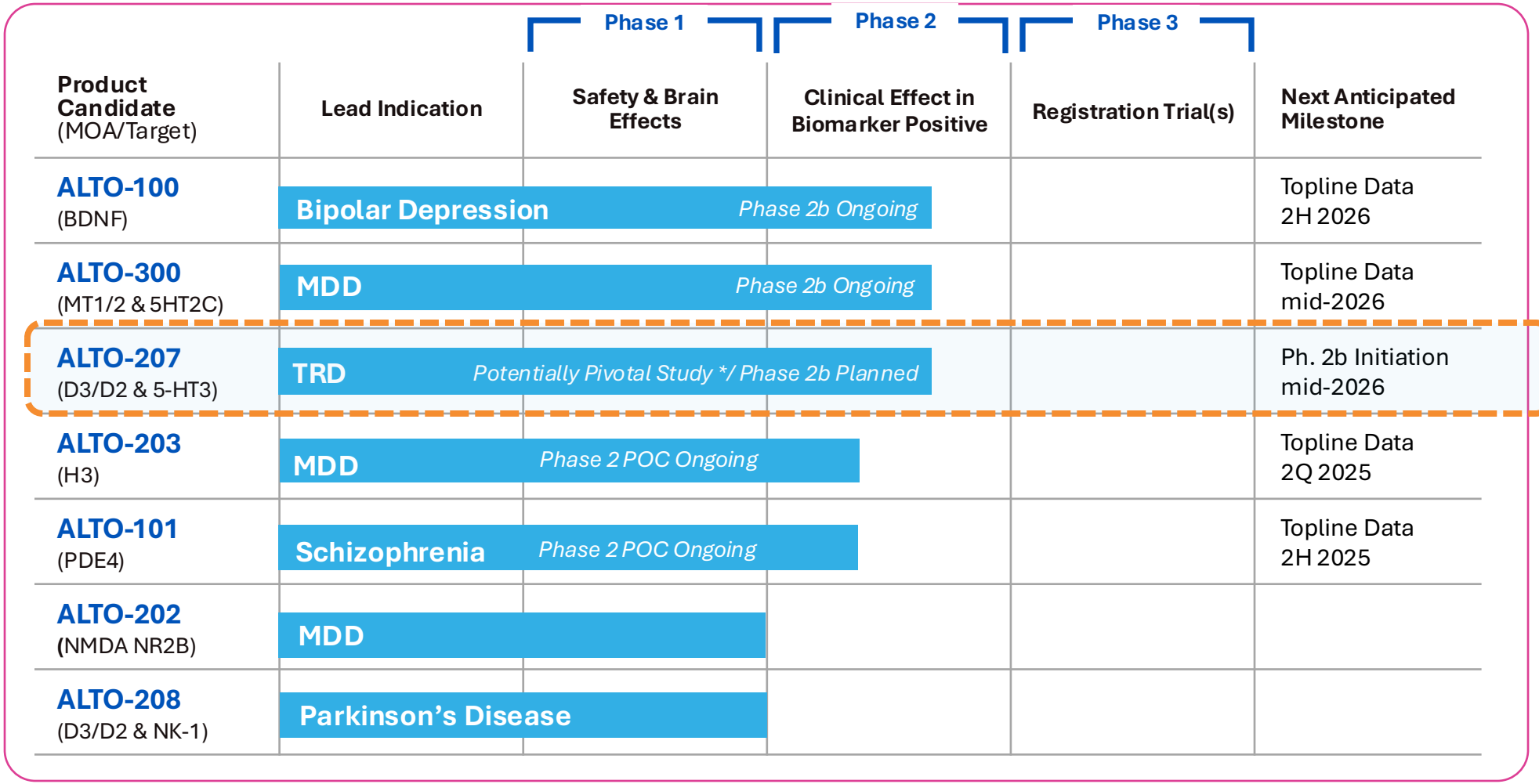
Including anticipated spend on potentially pivotal*/ Phase 2b TRD trial, Alto maintains cash runway into 2028; through 5 clinical data readouts

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**Study qualifying as pivotal is subject to FDA feedback and review of data*

First biomarker-driven pipeline for mental health conditions

Multiple independent programs leveraging our biomarker strategy to systematically reduce development risk; all programs remain on track to achieve upcoming milestones



Acquisition adds potentially late-stage/ potentially pivotal* TRD readout with clinically validated mechanism within current cash runway (into 2028)

*Study qualifying as pivotal is subject to FDA feedback and review of data

ALTO-207 (fka CTC-501) is a novel, clinically validated product candidate for a high need patient population

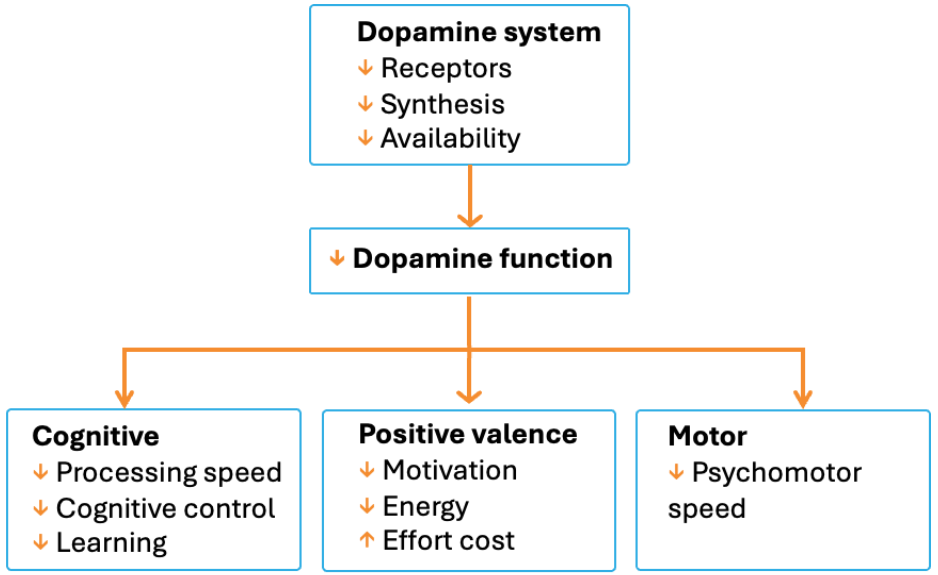
- Pramipexole has shown robust antidepressant effects but is limited by significant tolerability issues
- CTC-501 demonstrated clear safety benefits over pramipexole alone, achieving significantly higher doses in Phase 1, with 5x faster titration
- CTC-501 showed robust clinical effects in a randomized, placebo-controlled, Phase 2a trial; enabling a near-term potentially pivotal* / planned Phase 2b TRD trial with topline data expected in 2027
- Efficient and straightforward 505(b)(2) regulatory pathway provides a potentially shorter time to market
- Strong patent protection; validated commercial approach on combination products in psychiatry; compelling commercial case with substantial need in TRD

*Study qualifying as pivotal is subject to FDA feedback and review of data

ALTO-207 opportunity: biological and clinical rationale and data

Alto has been pursuing multiple complementary strategies to target reduced dopaminergic function in depression

Different "pro-dopaminergic" strategies may have varying effects across dopaminergic circuitry



Dopamine-relevant biomarkers

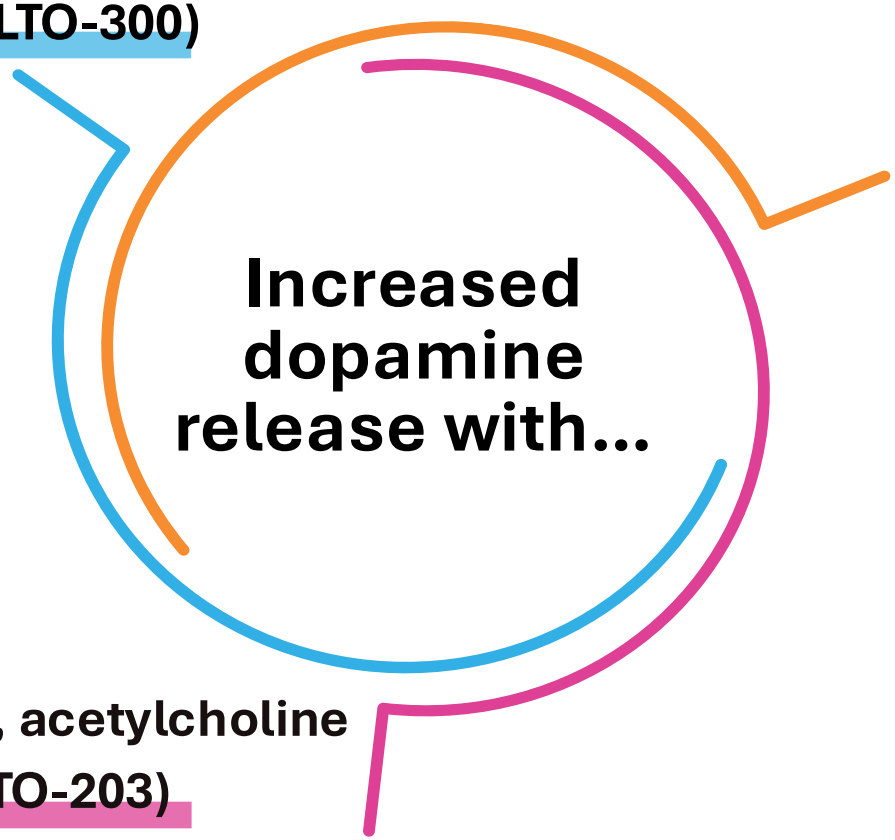
- Established EEG signatures and optimized behavioral measures, already deployed in trials

	Indirect control of dopamine release	Direct receptor stimulation
Advantage ✓	Modulate gain while preserving endogenous patterns Fewer dopamine-related AEs but more subtle effects	Drive supra-physiologic effects (e.g., D3/D2 receptors)
Key Challenge −	Functional effects depend on dopamine modulation strategy	Dose-related intolerance/AEs due to agonism
Alto's pipeline programs are designed to overcome existing challenges:	ALTO-203 ALTO-300	ALTO-204 ALTO-205 ALTO-206 ALTO-207

Potential differential effects and patient profiles for different dopamine-related products in depression

MT1/2 agonism and increased norepinephrine release (ALTO-300)

- Beneficial for sleep and circadian rhythms
- Well tolerated and well suited as an adjunctive treatment option



D3/D2 agonism (ALTO-207)

- Behavioral activation (“get up and go”)
- Anti-anhedonic
- Demonstrated clinical effect in TRD

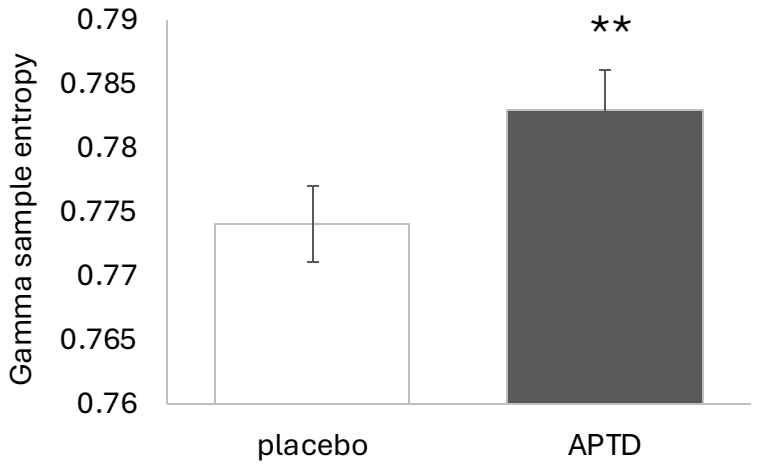
Increased norepinephrine, acetylcholine and histamine release (ALTO-203)

- Cognitive benefits
- Wake-promoting

Alto's EEG biomarkers have led to unique insights into dopaminergic mechanisms

Alto discovered that gamma sample entropy, an EEG measure that predicts ALTO-300 response, indexes dopaminergic activity **in humans**

↓ dopamine = ↑ gamma sample entropy



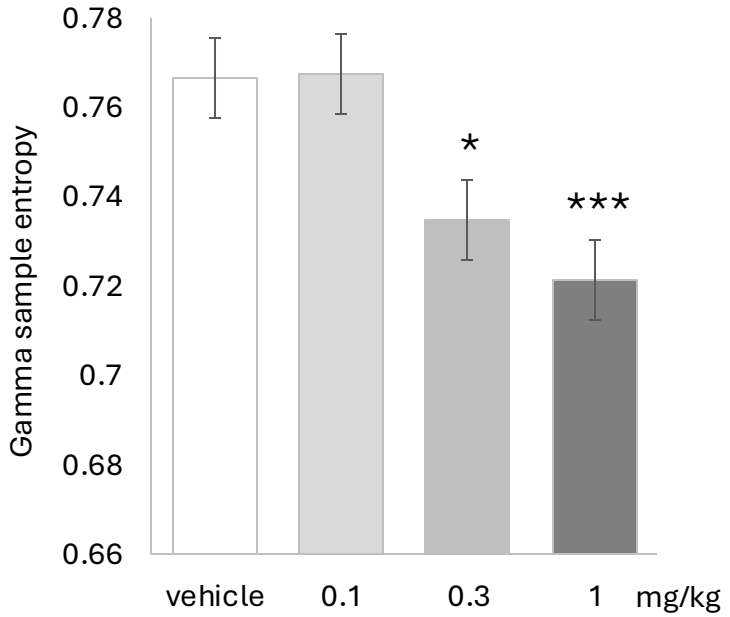
- Human dopamine depletion (n=12)
- Cross-over of dietary dopamine precursor depletion (APTD) or placebo

Sundar et al, SOBP 2025 (data from Larson, PLOS One, 2015)

Translational work in animals points to effects of the D3/D2 dopamine receptor agonist pramipexole on sample entropy:

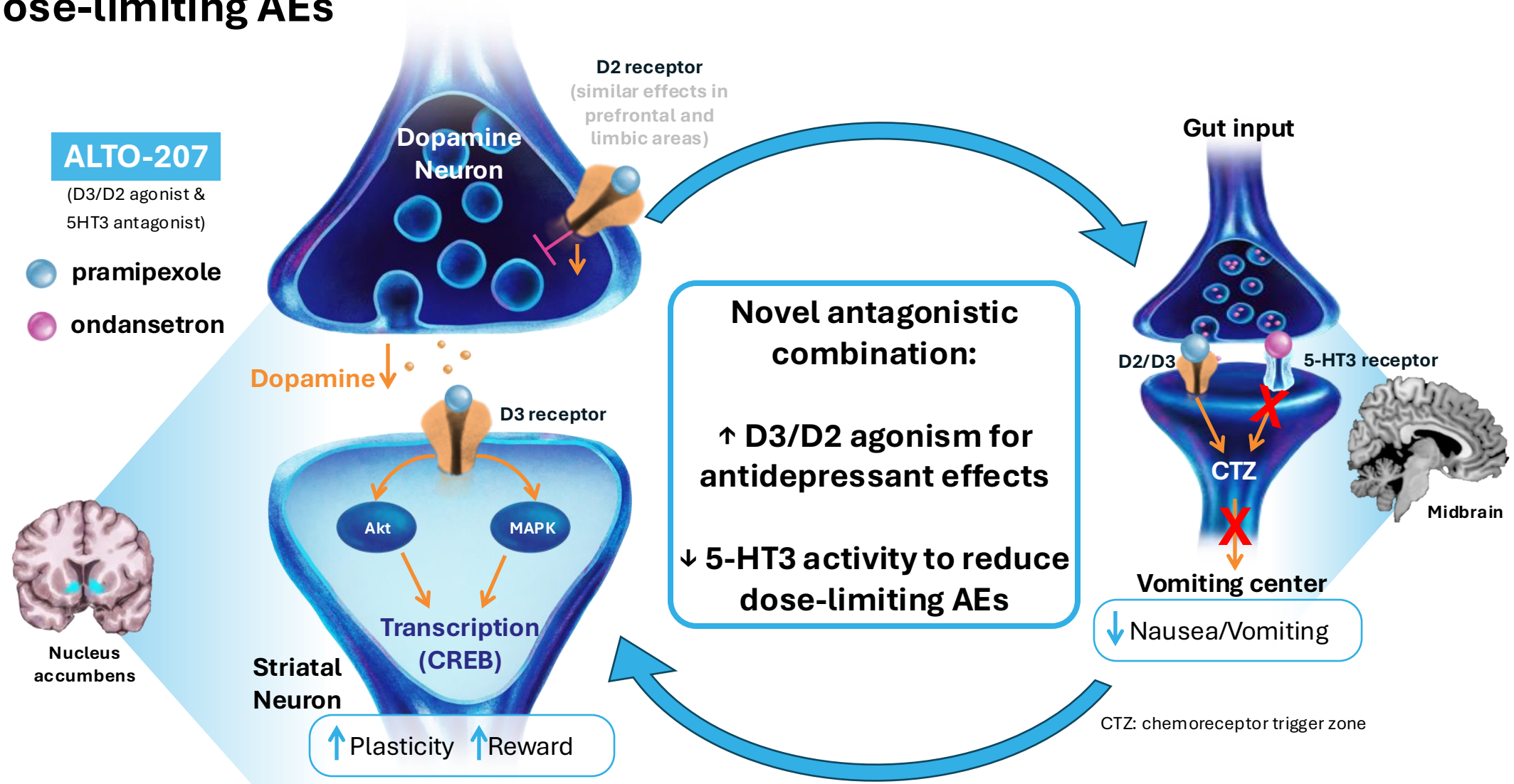
Pramipexole stimulates D3/D2 receptors

↑ D3/D2 activity = ↓ gamma sample entropy



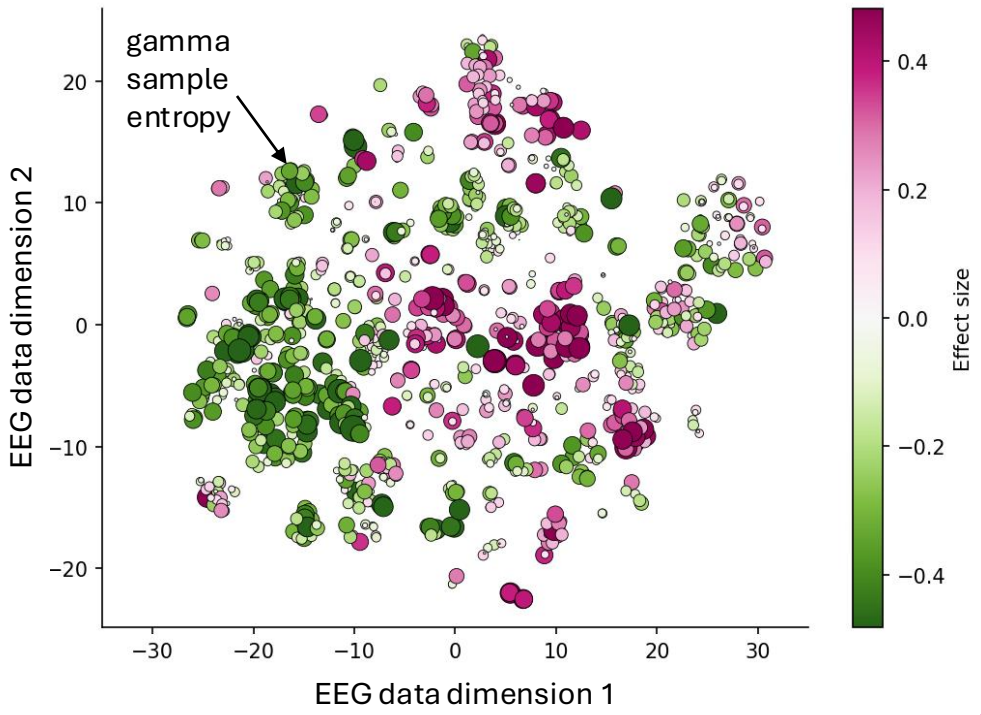
Vs. placebo or vehicle: * p<0.05; ** p<0.01, *** p<0.001

ALTO-207: combining a dopamine D3-preferring D3/D2 agonist with demonstrated antidepressant effects and 5-HT3 antagonist designed to reduce dose-limiting AEs



Leveraging a “digital twin” approach using a human pro-dopaminergic EEG signature to drive development of ALTO-207

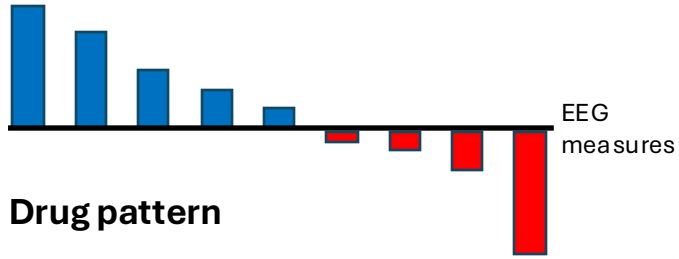
1 Defined a multivariate dopaminergic EEG signature



EEG “Digital Twin” discovery strategy to find clinical targets

2 **Rank order EEG features by dopaminergic stimulation**

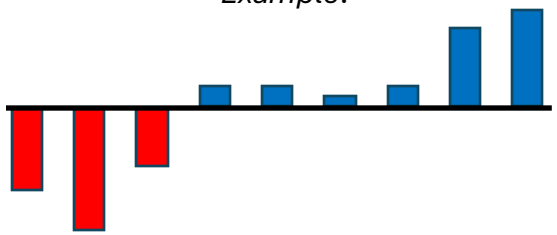
Example:



Drug pattern

3 **Match patient populations with opposite EEG signature**

Example:

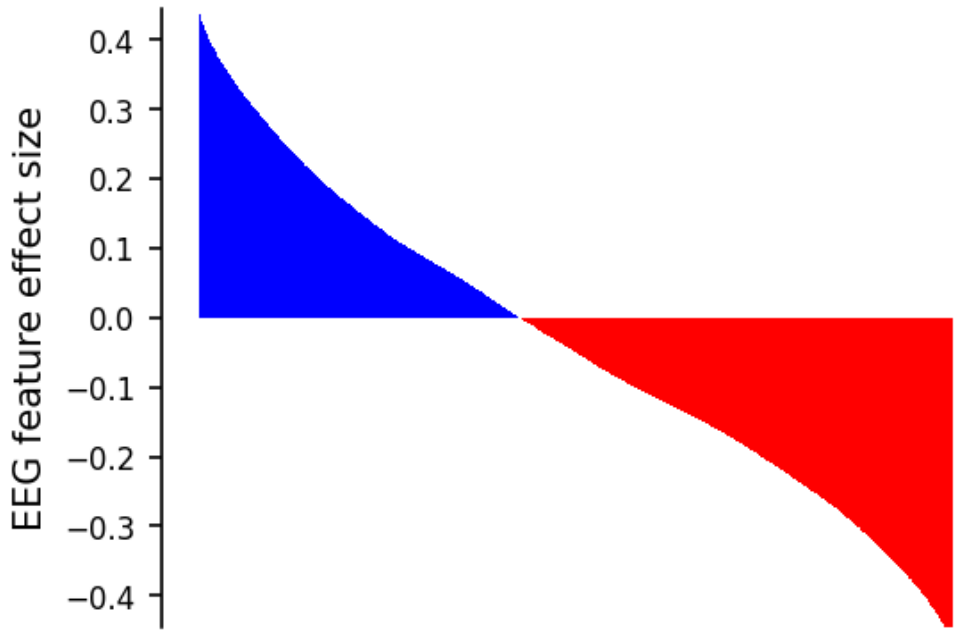


Target population: patient subgroup with pattern opposite of drug (demonstrating enrichment score (ES)<0)

Samart, Briefings in Bioinformatics, 2021

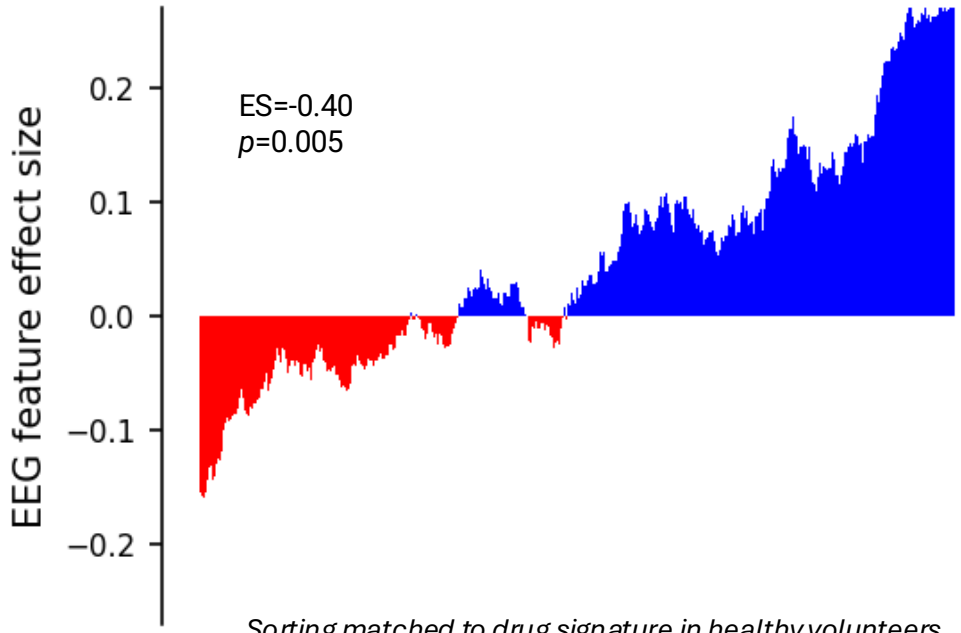
Dopaminergic drug digital twin signature is the opposite of the effects of dopamine depletion, validating the approach

Dopaminergic drug signature (post vs. pre)



Sorted from most increased to most decreased measure

Stronger digital twin signature in dopamine depleted state



Sorting matched to drug signature in healthy volunteers

Dopaminergic drug digital twin signature indexes key dopamine biology in humans

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ES: enrichment score (significantly < 0 indicates a pattern in a patient subpopulation that is opposite of the drug's EEG effects)

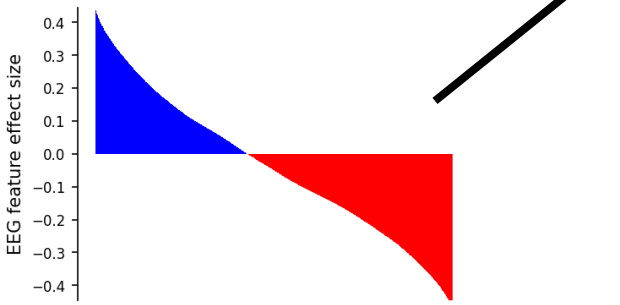
George, NeuroImage: Clinical, 2013; Cavanagh, Clinical Neurophysiology, 2018

Alto's digital twin strategy identifies TRD as target population along with dopamine-related behavioral and EEG biomarkers

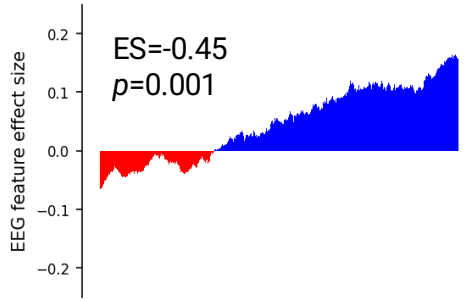
Dopamine-related biomarkers will be pre-specified as key secondary analyses

Stronger digital twin signature in MDD, especially those with TRD

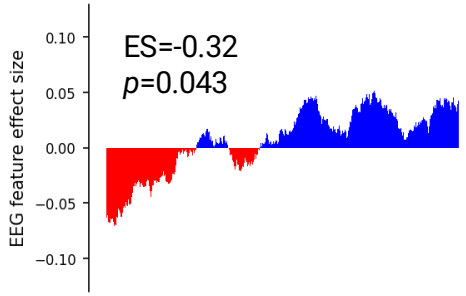
Dopaminergic digital twin



MDD (vs. healthy)

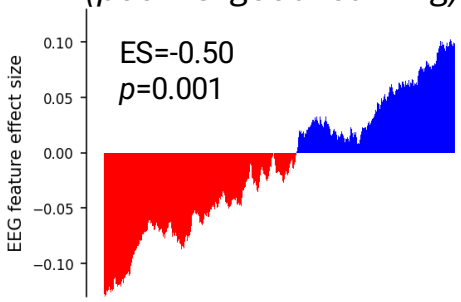


TRD (vs. non-resistant MDD)

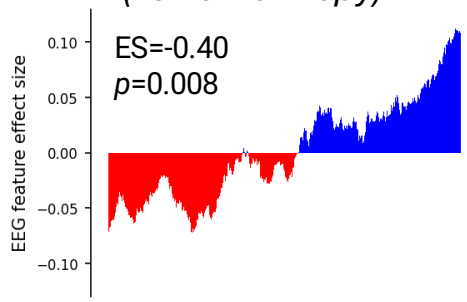


...and in MDD patients with biomarkers of low dopamine

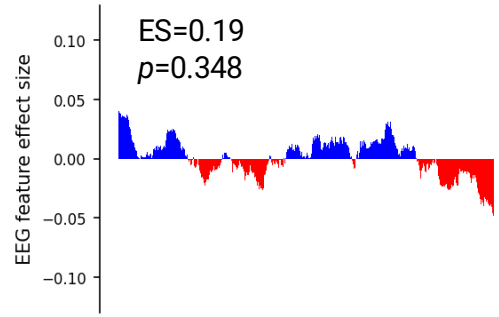
Poorer reward-based learning (poor vs. good learning)



High gamma sample entropy (vs. low entropy)



But no relationship to placebo response (good vs. poor response)



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George, NeuroImage: Clinical, 2013; Cavanagh, Clinical Neurophysiology, 2018

ALTO-207 opportunity: supported by strong pramipexole data

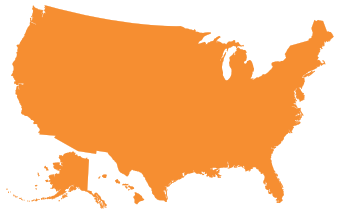
TRD market presents a significant opportunity

TRD is defined as MDD with inadequate response to at least 2 trials of antidepressant treatment



~1/3 of treated MDD patients are TRD – roughly 3M people in the US annually

Greater chronicity and disability, higher relapse rate, greater suicidality



Total annual economic burden of TRD in the US is $44B

Limited treatment options – antipsychotics and esketamine (as well as ECT, TMS)



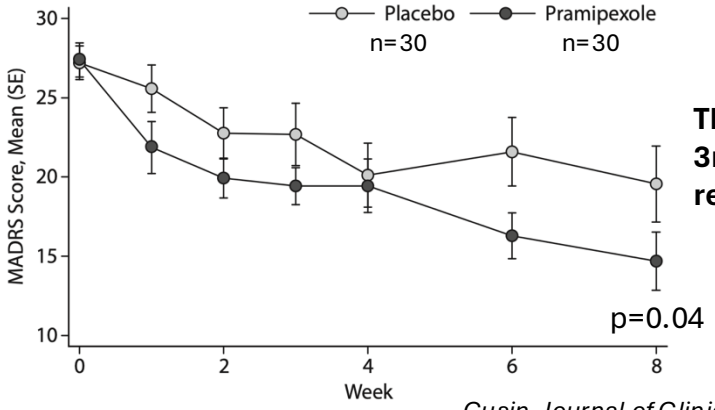
Annual cost of care for an individual with TRD is >$20,000 (1.5-2x higher than MDD)

Arnaud, Pharmacoeconomics, 2021; Zhdanava, Journal of Clinical Psychiatry, 2021; Johnston, Journal of Affective Disorders, 2019

Initial pramipexole trials showed antidepressant effect, but speed of titration and max dosage limited by nausea/vomiting

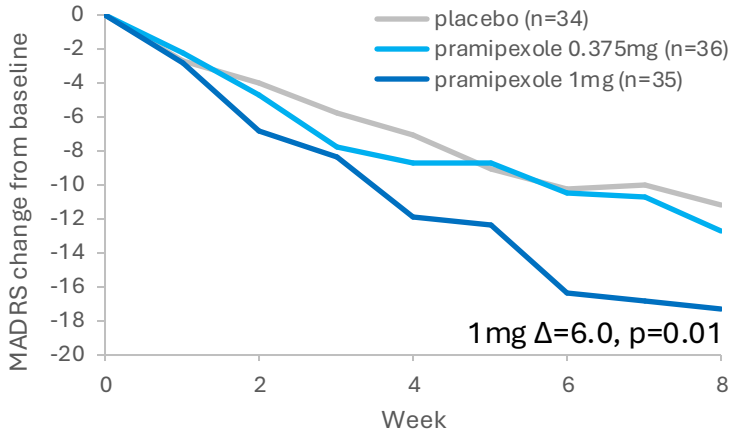
Evidence of clinical effect in small randomized trials

- Suggest minimally effective pramipexole dose is at 1-1.5mg
- Separation from placebo grew across weeks with dose escalation, suggesting potential for more rapid action



TRD study: aimed for 3mg/daily dose but only reached 1.35mg/day

Cusin, Journal of Clinical Psychiatry, 2013



MDD study

5mg* Δ=7.4

*5mg arm not shown due to 23+% greater dropout than placebo by week 8

Adapted from *Corrigan, Depression and Anxiety, 2000*

Efficacy limited by nausea/vomiting adverse events

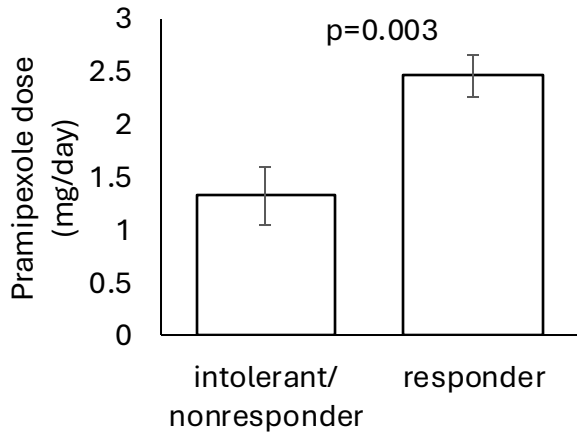
- AEs are dose-related
- FDA label and clinical trials required slow titration to mitigate AEs, but still dose-limiting for many, resulting in:
  - Inconsistent dosing across patients
  - Many dropouts
  - Insufficient overall exposure
  - Difficulty reaching the higher doses some require

Category	Placebo	Pramipexole 0.375 mg	Pramipexole 1 mg	Pramipexole 5 mg
Total number of patients	34 (100)	36 (100)	35 (100)	33 (100)
Number of patients with AEs	28 (82.4)	34 (94.4)	30 (85.7)	31 (93.9)
Nausea	7 (20.6)	9 (25.0)	16 (45.7)	25 (75.8)
Vomiting	2 (5.9)	0	4 (11.4)	13 (39.4)

Corrigan, Depression and Anxiety, 2000

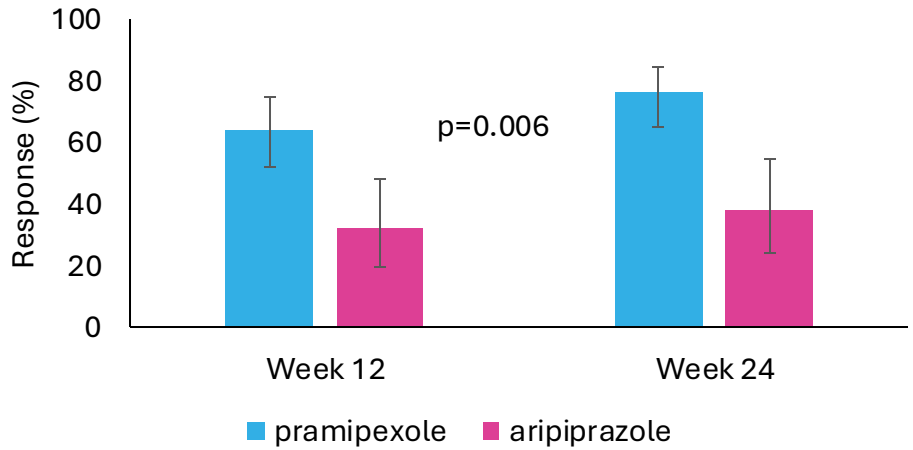
Growing body of compelling data shows robust clinical effect of pramipexole in TRD

- Treatment resistant case series (n=42)
- Responders (76%) achieved a higher dose (2.46mg/day vs. 1.33mg/day), with effects persisting over 16 months
- Slowest titration observed across younger adult patients due to AE rate (dopamine receptors decrease with age)



Fawcett, American Journal of Psychiatry, 2016

- Observational study in TRD compared pramipexole (n=81) or aripiprazole (n=51)
- Pramipexole dose achieved 1.49mg/daily
- Higher response rate with pramipexole (64% at 12 weeks)
  - The average placebo response in TRD studies is 22% *(Jones, JAMA Network Open, 2021)*
- Superiority of pramipexole persisted for 12 months
- No difference in safety at the 12- or 24-week time points



Tundo, Biomedicines, 2024

Clinical effect in TRD is possible but requires slow titration to higher target doses

Department of Psychiatry

Medical Sciences Division

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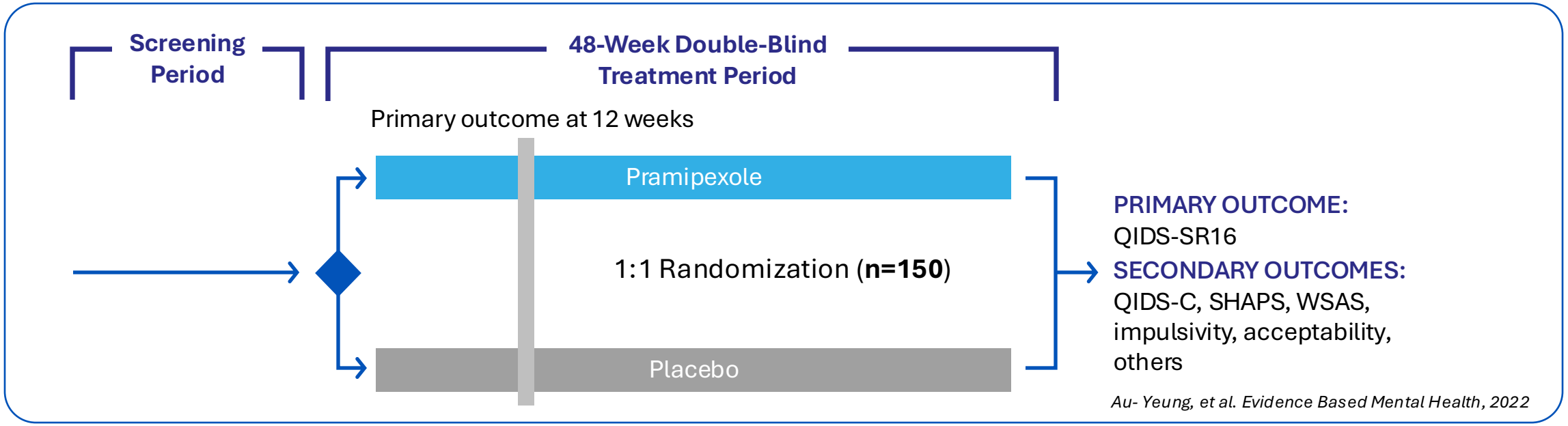
Michael Browning DPhil, MB.BS, MRCP, MRCPsych
Professor of Computational Psychiatry,
University of Oxford

NIHR | National Institute for Health and Care Research

NIHR | Oxford Health Biomedical Research Centre

PAX-D study provides strong validation of mechanism in TRD

Objective: evaluate pramipexole clinical effect in TRD and determine if slow titration to a higher dose is worth the high AE rate



- Targeted titration of pramipexole titrated to 2.5mg over 28 days
- Study conducted across network of 9 clinical sites in UK (NHS)
- Treatment was adjunctive to failed antidepressant

Quick Inventory of Depressive Symptomatology-self-assessment (QIDS-SR-16); QIDS-clinician rated (QIDS-C); Snaith-Hamilton Pleasure Scale (SHAPS); Work and Social Adjustment Scale (WSAS)

Baseline characteristics: highly TRD population

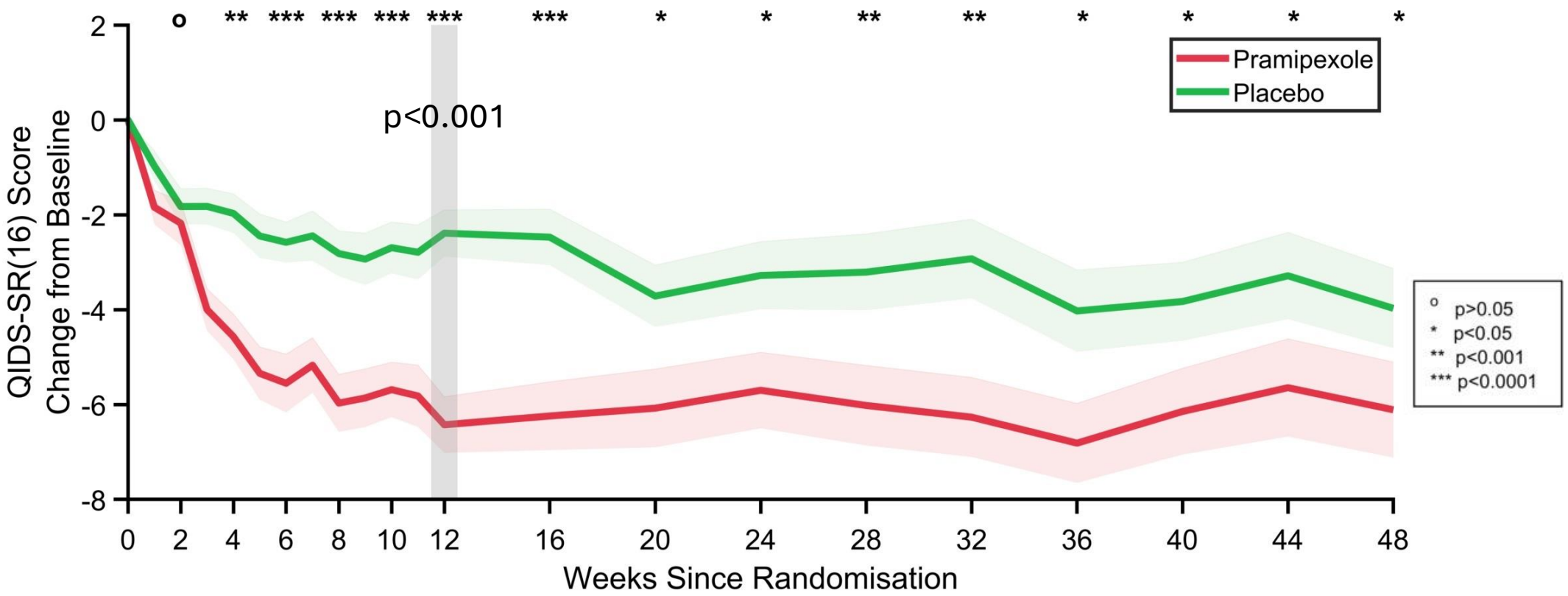
		Pramipexole (n= 75)	Placebo (n= 75)
Demographic characteristics			
Age (years)		43·9 ± 15·2	45·9 ± 12·7
Female sex-- n (%)		41 (54·7%)	43 (57·3%)
Body Mass Index		30·6 ± 7·54	29·8 ± 6·4
Psychiatric history			
Duration current episode in years -- median (IQR)		8·0 (2·5 to 15·0)	10 (5·0 to 20·0)
Failed pharmacological treatments for current episode-- no		3·2 ± 1·4	3·7 ± 2·1
Antidepressant medication at randomisation by class‡	SSRI	41 (54·7%)	40 (53·3%)
	SNRI	19 (25·3%)	21 (28·0%)
	TCA	6 (8·0%)	1 (1·3%)
	MAOI	2 (2·7%)	1 (1·3%)
	Other	21 (28·0%)	24 (32·0%)
Depression and associated symptom scores			
QIDS-SR_{16} Mean		16·4 ± 3·4	16·2 ± 3·5
QIDS-C		15·8 ± 3·4	15·4 ± 3·2
SHAPS		7·8 ± 3·9	7·8 ± 3·7
GAD-7		11·7 ± 5·3	11·8 ± 5·3
WSAS		25·2 ± 8·1	24·7 ± 7·4

Highly refractory population

Moderate – severe depression (QIDS ≥ 16 = severe)

Pramipexole led to a robust improvement in depression

Large effect size (Cohen's d=0.89)



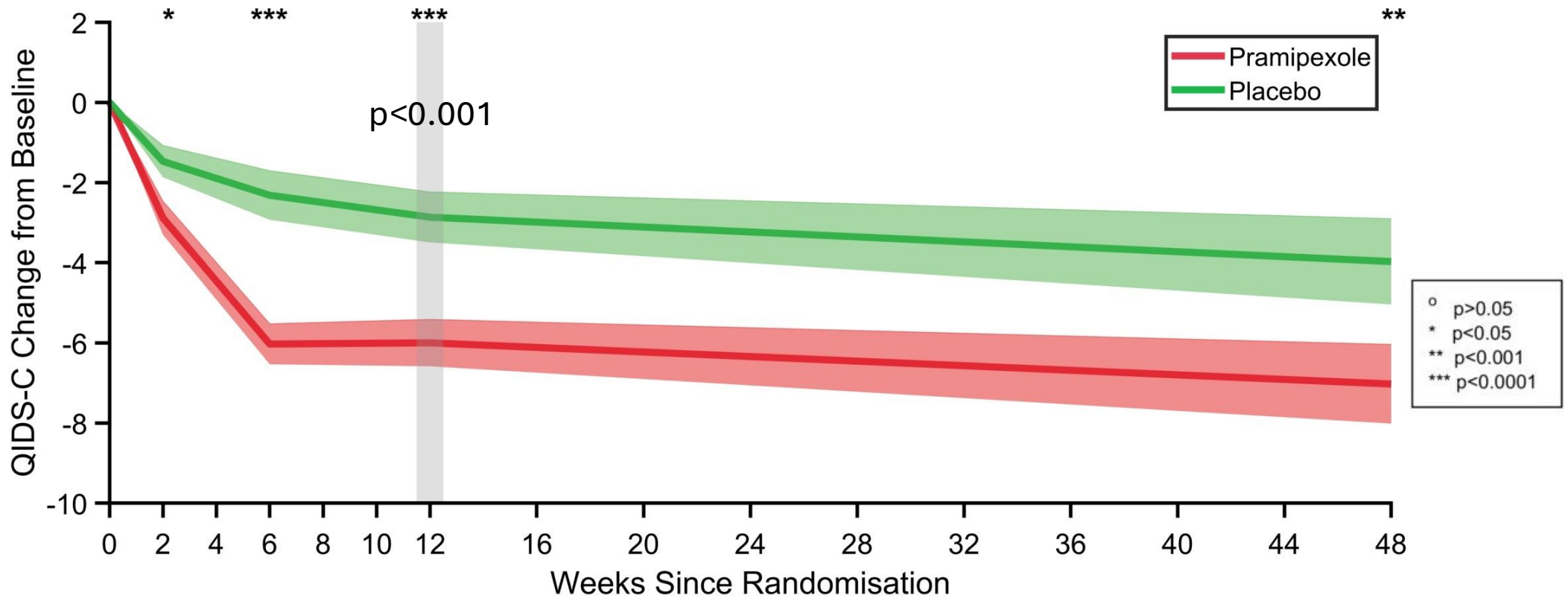
QIDS-SR$_{16}$ change converts to a MADRS Δ of 7.38 points*

* Conversion to MADRS from Carmody, Journal of Affective Disorders, 2006

Browning, under review

Consistent robust effect on clinician-rated QIDS

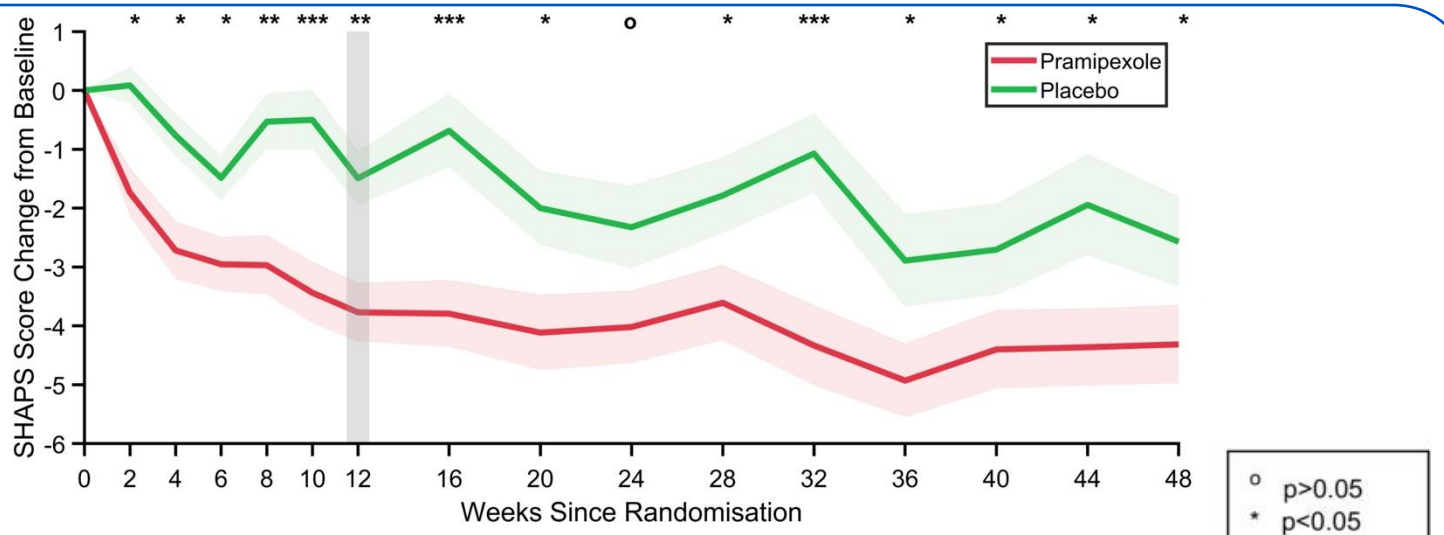
(Cohen's d=0.67, p<0.001)



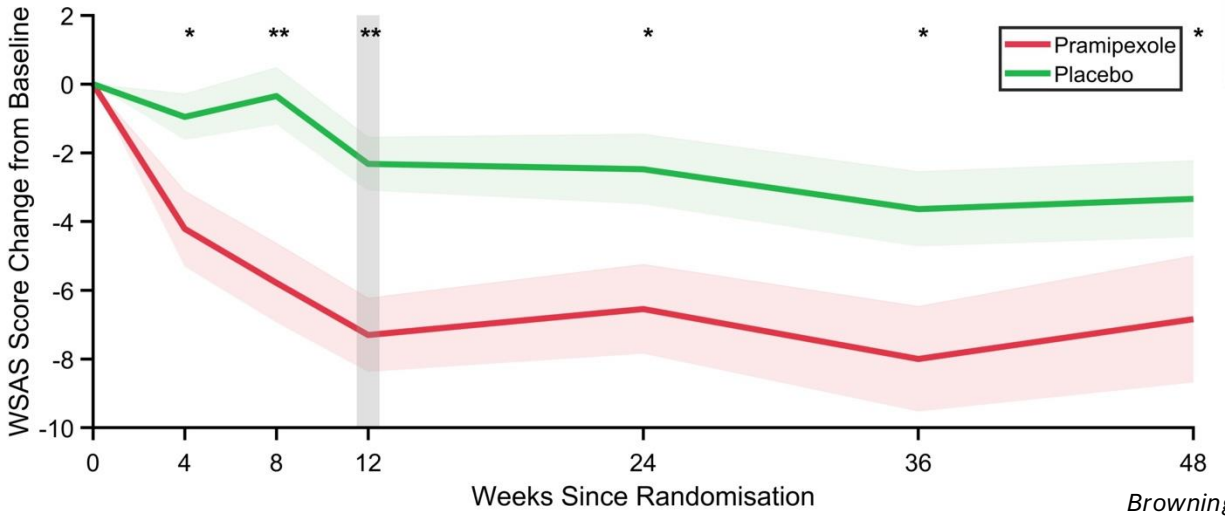
Browning, under review

Pramipexole similarly improved anhedonia and functioning

Anhedonia: SHAPS



Functioning: WSAS



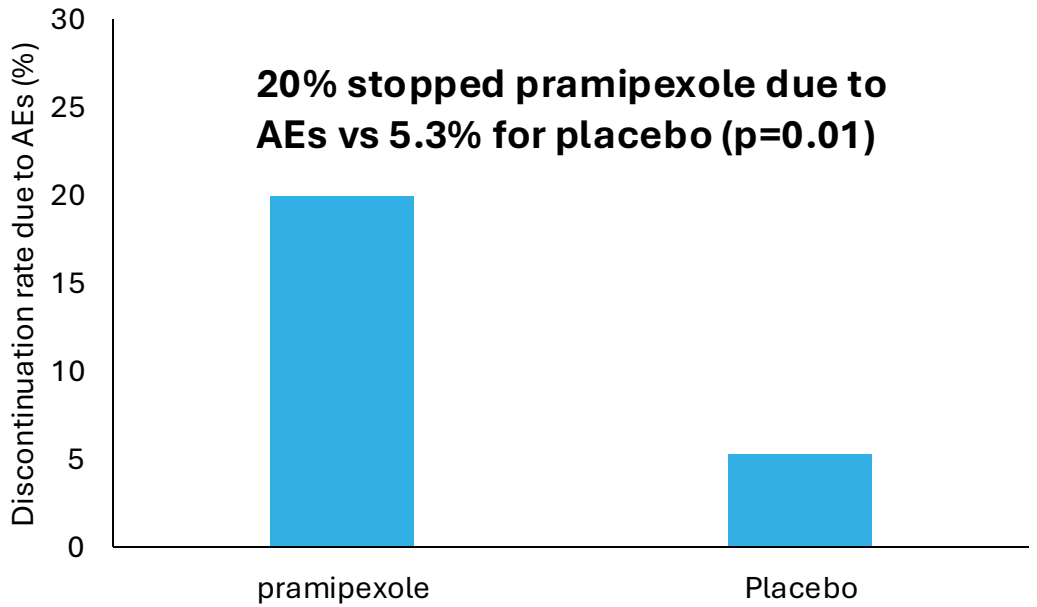
Suicidality and anxiety similarly improved

Browning, under review

Snaith-Hamilton Pleasure Scale (SHAPS); Work and Social Adjustment Scale (WSAS)

Tolerability: in line with expected pramipexole AE pattern

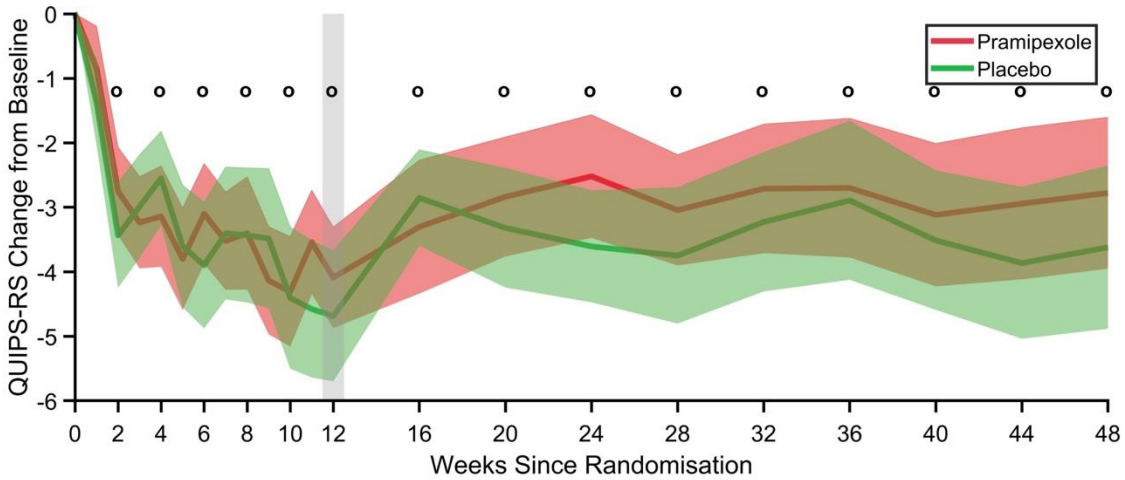
Adverse Event	Pramipexole N=75	Placebo N=75
	Number (%)	
Adverse events occurring in ≥10% of either group		
Nausea	50 (67)	31 (41)
Headache	47 (63)	37 (49)
Dizziness	42 (56)	27 (36)
Vomiting	22 (29)	9 (12)
Somnolence	18 (24)	6 (8)



High AE rates and significant dropout rates suggest the need for improved tolerability profile with ability to reach therapeutic dose more quickly

Tolerability: no increase in impulsivity

- Reports of increase in impulse control disorders in Parkinson's patients receiving dopamine agonists
- However, this is in the context of a highly perturbed dopaminergic system
- PAX-D data using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIPS-RS) showed no increase in impulsivity in TRD
- Raises the possibility that impulse control side effects in Parkinson's disease are related to its pathophysiology, not a general drug effect



Browning, under review

PAX-D conclusions point to the opportunity with ALTO-207

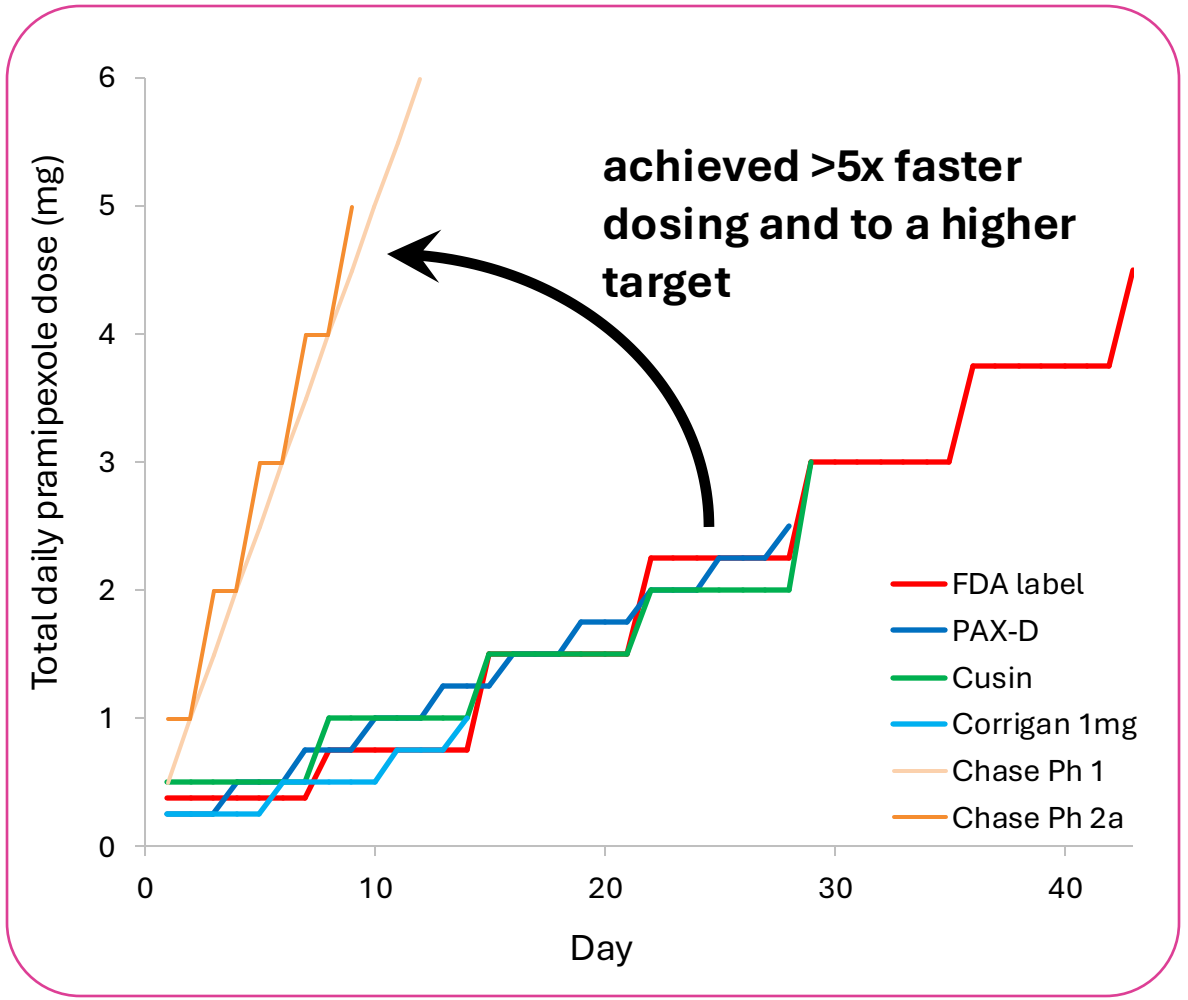
- Pramipexole was highly effective in TRD, while not head-to-head comparison, results suggested a greater effect than any other TRD treatment
- Generally, pramipexole requires slow titration due to dose-limiting AEs; clinicians have not widely adopted pramipexole off-label
- Due to tolerability challenges its use is limited, but shows long-term clinical effect and safety in those who tolerate
- A next generation approach would:
  - Achieve greater tolerability more consistently across patients, especially at higher doses
  - Accelerate titration
  - Achieve rapid effect
  - Leverage a targeted approach to identify who derives the greatest benefit (e.g., biomarkers)

CTC-501 (n.k.a. ALTO-207) clinical development builds on previously demonstrated:

- Rapid dose escalation to higher targets
- Large clinical effect sizes

n.k.a.: now known as

CTC-501 (n.k.a. ALTO-207): designed to achieve rapid antidepressant effect



n.k.a.: now known as

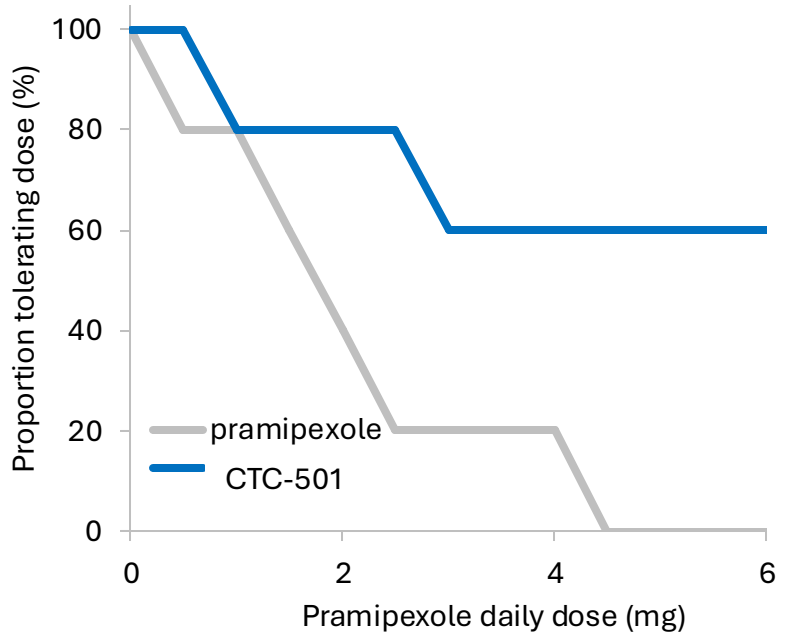
CTC-501 (n.k.a. ALTO-207) combination approach achieved higher pramipexole doses faster and more consistently

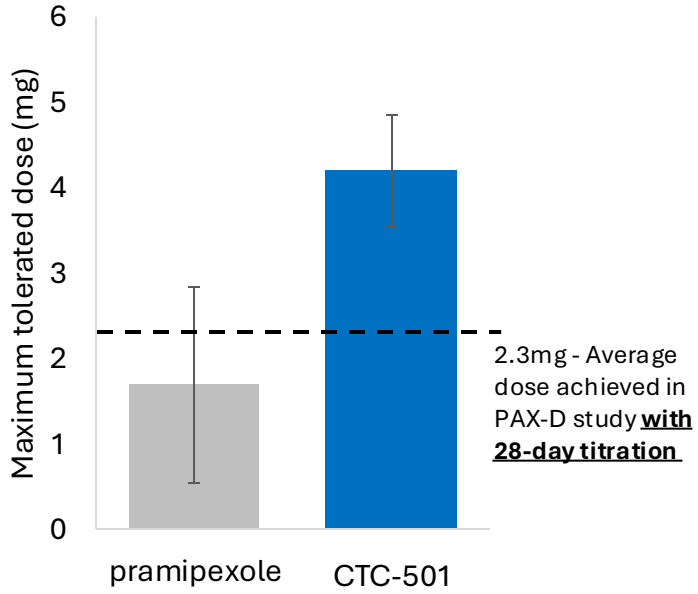
Novel combination supported by Phase 1* safety data

Results:

- Achieved a **2.5-fold or greater increase** in the pramipexole maximum tolerated dose with addition of ondansetron vs. pramipexole alone
- **60% tolerated max dose of CTC-501** (6mg pramipexole), achieved within 12 days
- Supports ability to more quickly achieve a higher and more consistent dose level than pramipexole alone

≥2.5x increase in pramipexole tolerability

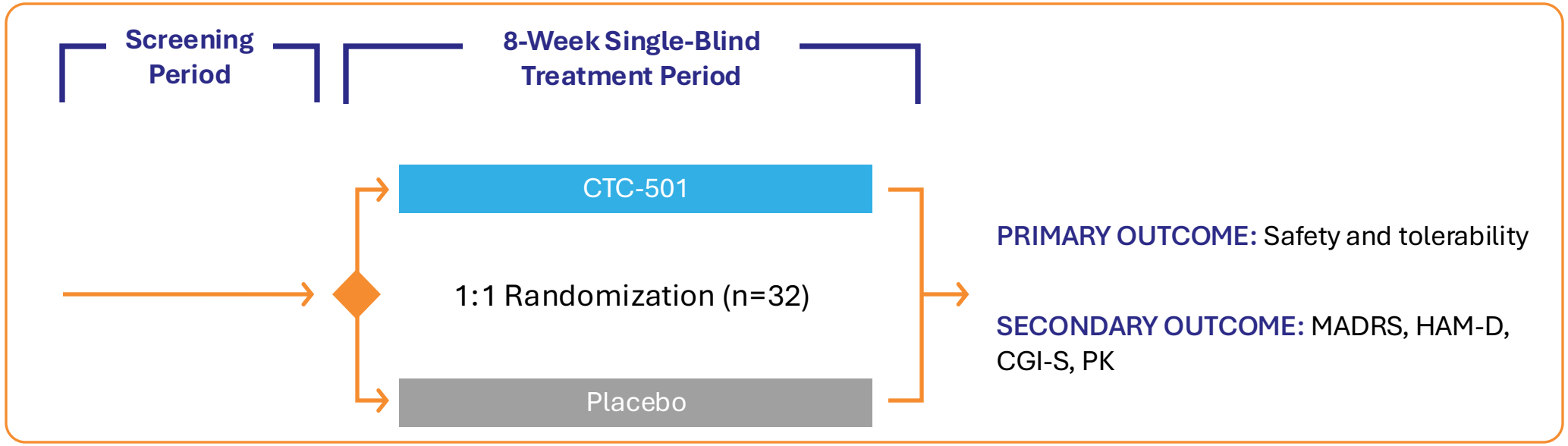




*Chase Therapeutics sponsored trial

n.k.a.: now known as

Completed CTC-501 (n.k.a. ALTO-207) Phase 2a trial in MDD



- **Inpatient titration**: 1 mg every 1-2 days to maximum tolerated dose or maximum allowed dose of 5 mg/day
- **Titration period and dose achieved**: 7.9 (SD 2.3) days to achieve 4.1mg (SD 1.8) daily dose
- **Percentage achieving max 5mg/day dose**: 67% (77% after initial dosing schedule adjustment)
- **Outpatient maintenance:** remainder of 8-week treatment period

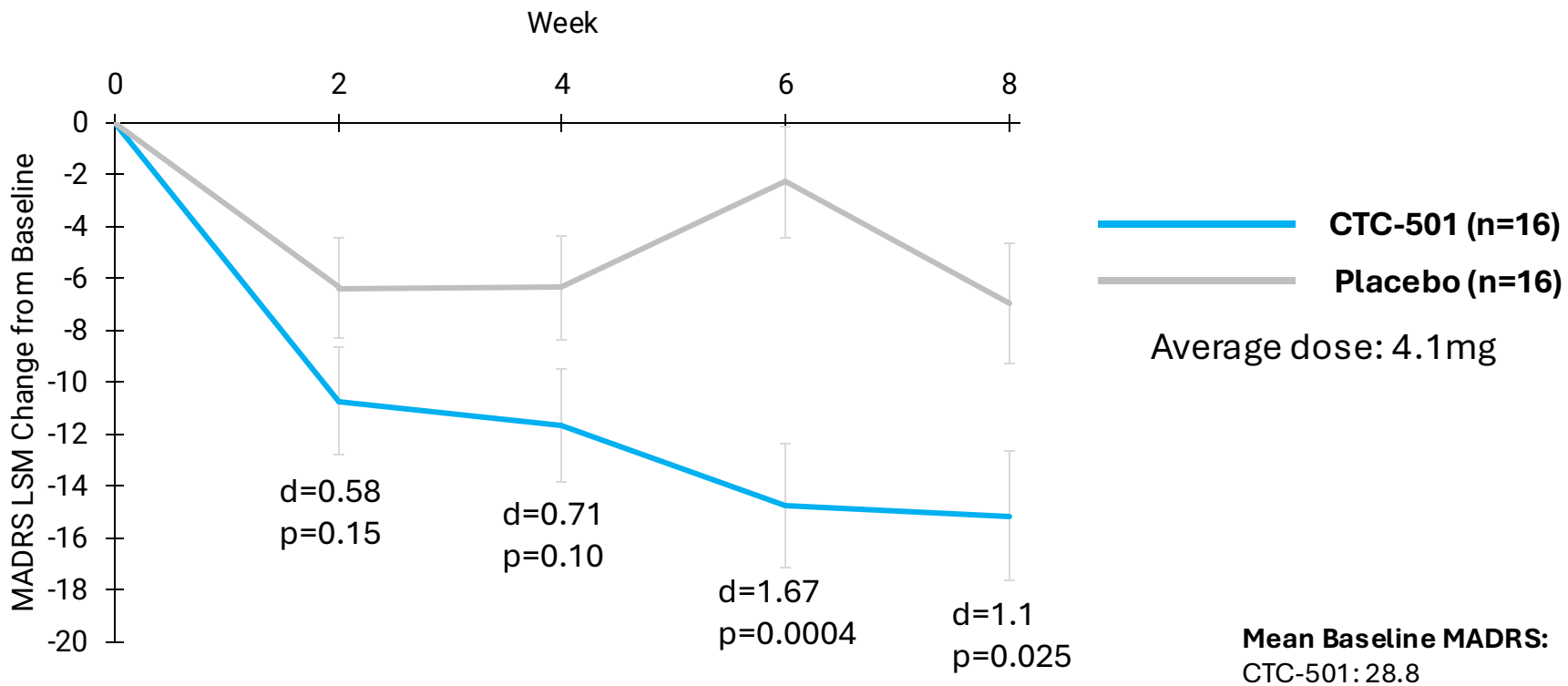
*Chase Therapeutics sponsored trial

n.k.a.: now known as

Phase 2a trial of CTC-501 (n.k.a. ALTO-207) in MDD: MADRS

Significantly greater reduction in depressive symptoms compared to placebo

MADRS – Change from Baseline



Mean Baseline MADRS:
CTC-501: 28.8
Placebo: 28.2

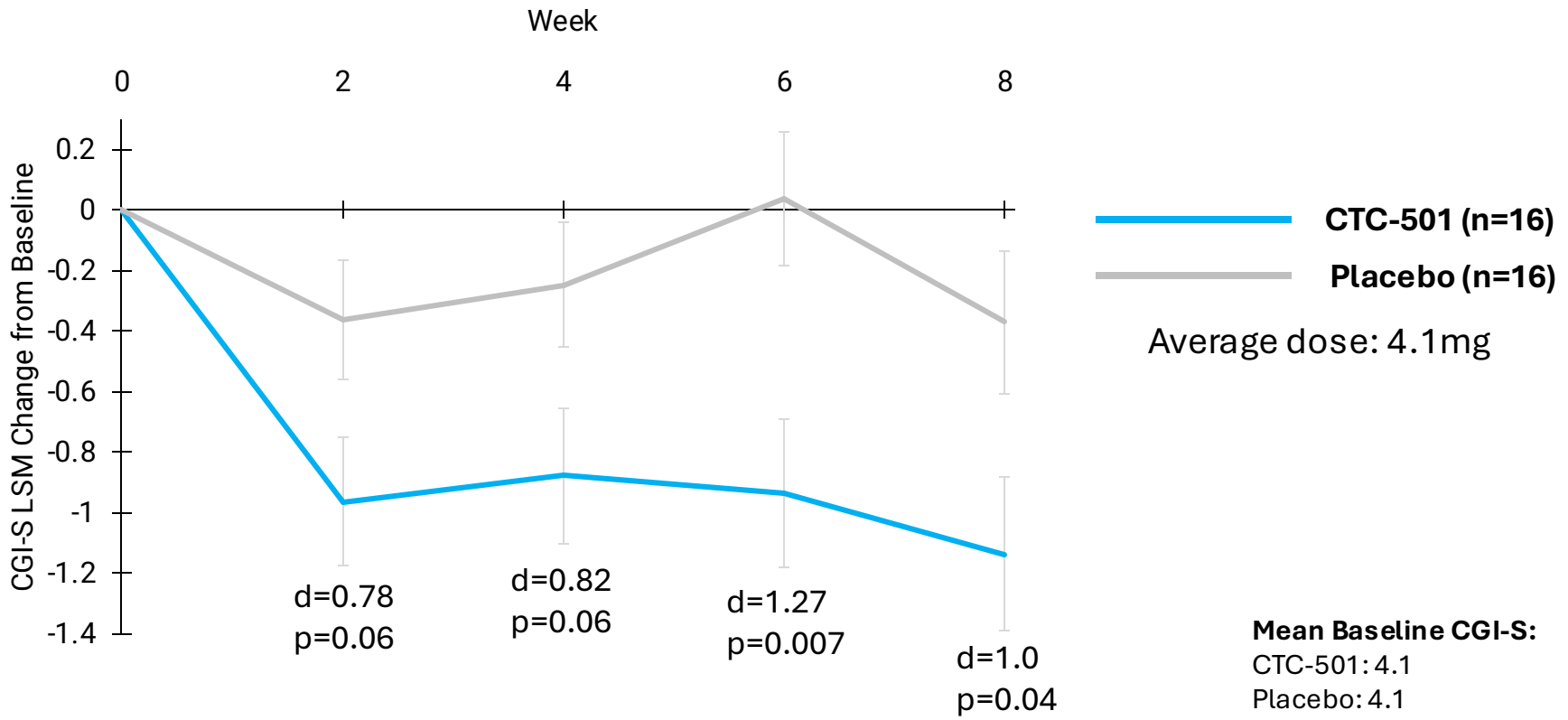
*Chase Therapeutics sponsored trial

n.k.a.: now known as

Phase 2a trial of CTC-501 (n.k.a. ALTO-207) in MDD: CGI-S

Significantly greater reduction in illness severity compared to placebo

CGI-S – Change from Baseline



*Chase Therapeutics sponsored trial

n.k.a.: now known as

Phase 2a trial of CTC-501 (n.k.a. ALTO-207) in MDD confirmed favorable safety and tolerability profile

Nausea and vomiting were the most common AEs – all were mild to moderate

Post-titration AEs*

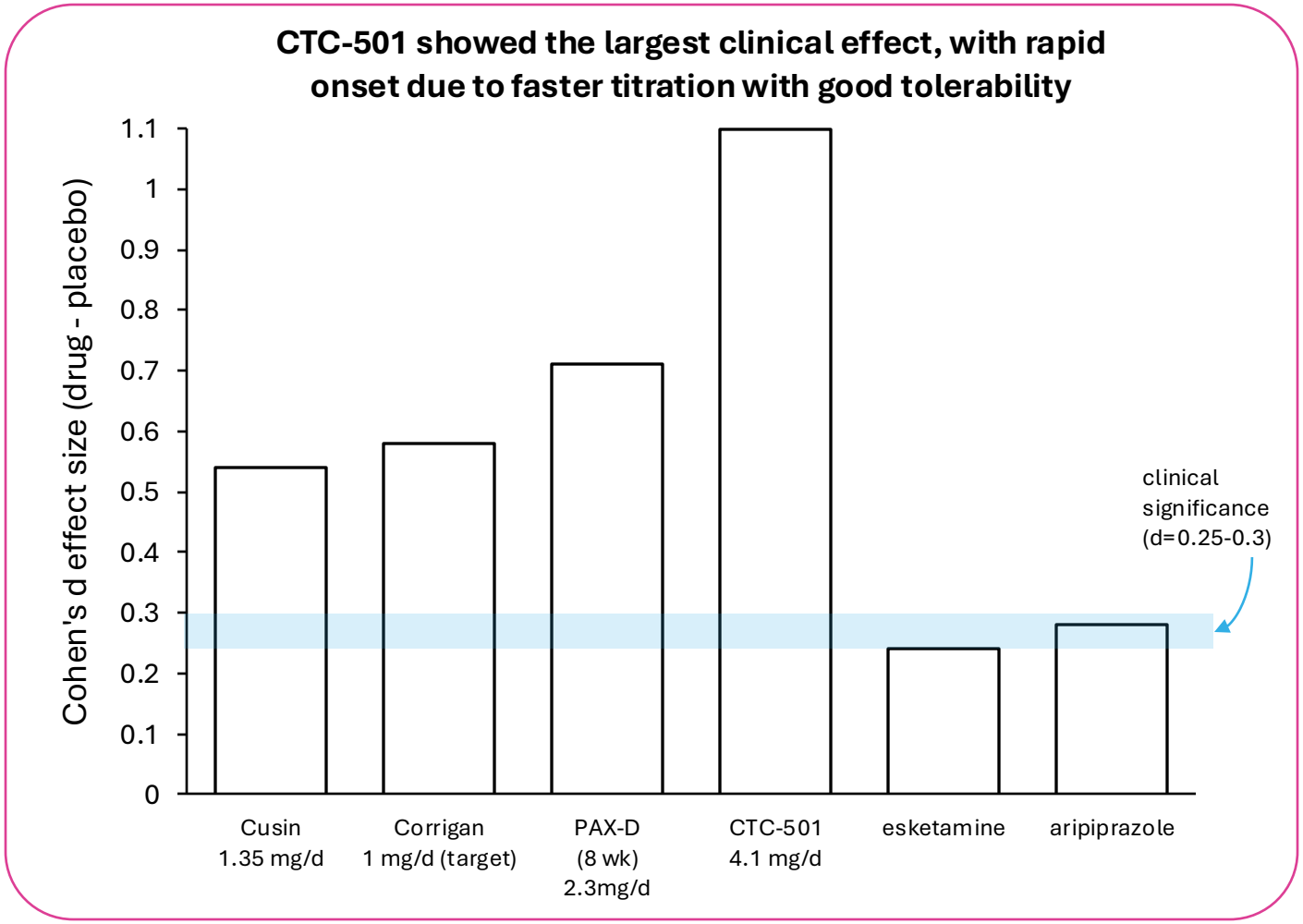
	CTC-501 (N=13)		**Placebo** (N=15)	
	Related	**Unrelated**	**Related**	**Unrelated**
Nausea	2 (15%)	2 (15%)	0 (0%)	2 (13%)
Vomiting	1 (8%)	3 (23%)	0 (0%)	2 (13%)
Headache	1 (8%)	0 (0%)	0 (0%)	0 (0%)
Sleepiness	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Titration AEs are related to Chase's maximum tolerated dose-based titration schedule, which Alto aims to further optimize in planned future trials

*Chase Therapeutics sponsored trial

n.k.a.: now known as

CTC-501 (n.k.a. ALTO-207): designed to achieve rapid antidepressant effect



Note: The results shown above are not based on head-to-head trials between the products or product candidates. Study designs and protocols differed, and results may not be comparable.

** Effect sizes for Cusin and Corrigan data estimated from available information; Cusin, Journal of Clinical Psychiatry, 2013; Corrigan, Depression and Anxiety, 2000; Wang et al., Medicine, 2023; Jawad et al., Exp Op Drug Saf, 2022; efficacy of other adjunctive antipsychotics is similar to aripiprazole (Wang et al)*

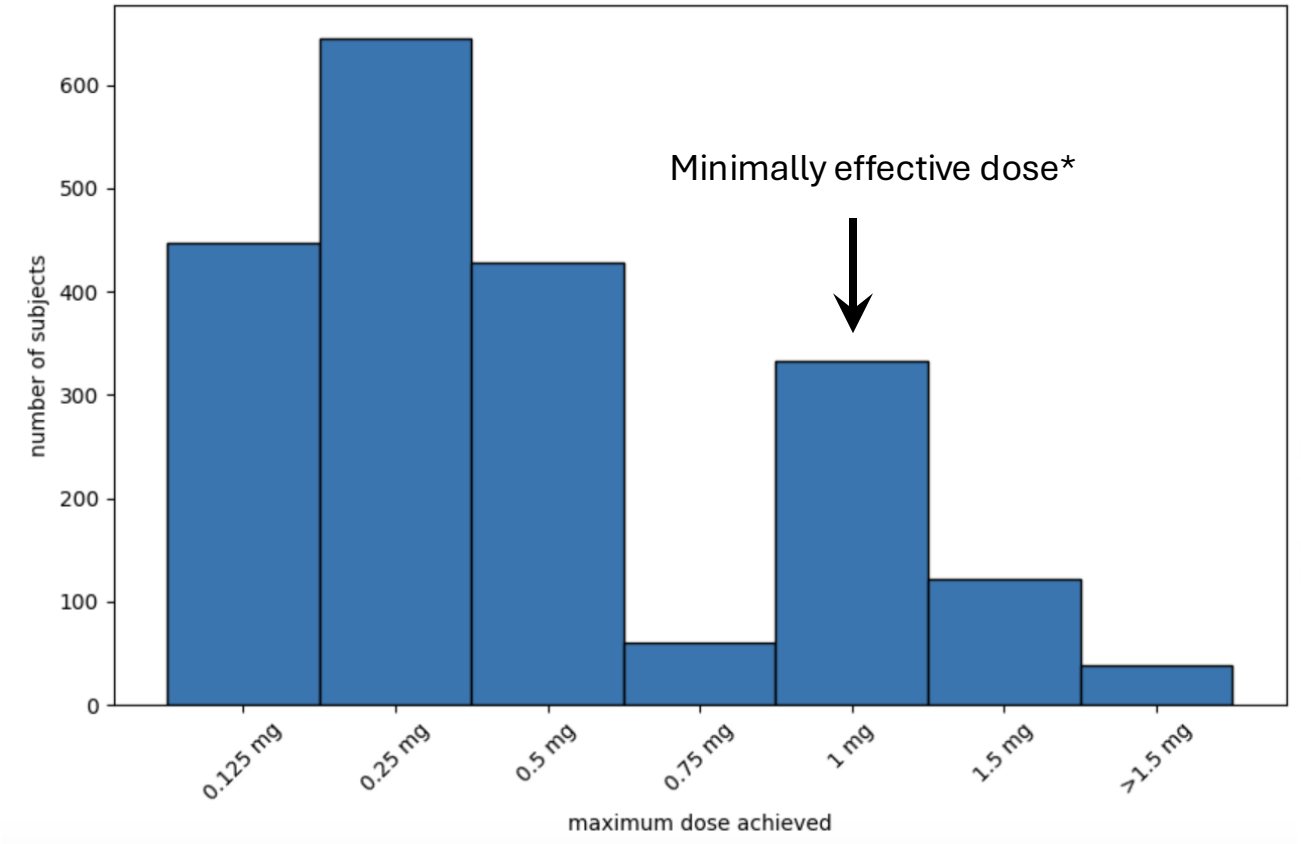
Real world prescribing of pramipexole in MDD shows ***very slow titration*** and few get to a therapeutic dose level, limiting use

Data drawn from NIH's *All of Us* dataset (N=633,547), focusing on those with MDD (N=113,666)

- 1.8% treated with pramipexole (N=2,093)
  - 23.7% achieved ≥1mg/day
  - 1.5% achieved >1.5mg/day

- Suggests the vast majority of patients are treated with sub-therapeutic doses and very few achieve TRD-level dose targets
- Likely limited by AEs and practical difficulty of titration in clinical practice

- Average time between dose escalation: **273 days**



*Cusin et al and Corrigan et al suggest 1-1.5mg is minimally effective dose

ALTO-207 positioned for potential Phase 2b/pivotal* success

- Highly compelling evidence for the clinical effect of pramipexole in TRD, with principal limitation being dose-related intolerability (which motivated development of CTC-501)
- Completed Phase 1 study demonstrated significantly improved tolerability with 5x faster dose escalation
- Phase 2a placebo-controlled study met its primary and secondary endpoints, showing large clinical effect sizes
- Planned collaboration with PAX-D sites, building on their highly successful trial outcome

Alto expects to initiate a Phase 2b (potentially pivotal design*) trial in TRD in 1H 2026 with TLD in 2027

Study qualifying as pivotal is subject to FDA feedback and review of data

Intended regulatory strategy makes use of biomarkers

Dopamine-related biomarker strategy

- Will focus on both clinical effect and tolerability
- Biomarkers will be pre-specified key secondary measures for the Phase 2b trial and verified in Phase 3 as complementary enrichment markers
- Leverage Alto's dopamine-related EEG and behavioral assessments already employed across studies

Regulatory considerations

- Anticipate a regulatory path with broad TRD approval as well as potential for an enrichment marker to identify patients with even greater effect[(1)]
- Biomarker strategy builds on Alto's FDA interactions on enrichment markers in the ALTO-100 program
- 505(b)(2) regulatory path enables streamlined development and potentially shorter time to commercialization

ALTO NEUROSCIENCE

[(1)]Based on Chase's interactions with the FDA to date; intended regulatory strategy is subject to FDA feedback

**Study qualifying as pivotal is subject to FDA feedback and review of data*

Stanford MEDICINE

Department of Psychiatry and Behavioral Sciences

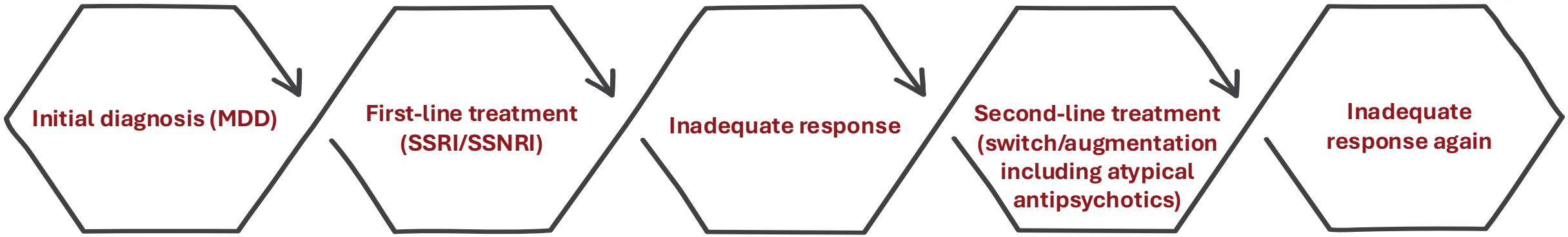
Stanford University



Alan F. Schatzberg, MD

Kenneth T. Norris, Jr. Professor of Psychiatry and Behavioral Sciences, Stanford University

Patient journey in TRD



- Patients who do not achieve a satisfactory response after undergoing at least two adequate trials of different antidepressant medications are typically classified as having TRD
- Patients are then referred to psychiatric specialists for more comprehensive evaluation and management
- Treatment plans include esketamine (Spravato) and may expand to non-pharmacological interventions such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS)

ALTO-207 combination approach: opportunity for rapid onset, improved tolerability, and greater convenience

- ✓ **Rapid onset and faster titration**: can reduce patient distress and improve compliance
- ✓ **Safety and tolerability**: well-tolerated and orally administered making it easier to initiate and maintain in outpatient care
- ✓ **Mechanistic differentiation**: offers benefits to patients who haven't responded to conventional antidepressants, antipsychotics or esketamine through a distinct mechanism
- ✓ **Built-in synergy**: single prescribable agent **simplifies treatment strategy and monitoring** compared to manual slow titration of pramipexole (requiring significant hands-on clinician time) or even augmentation with ondansetron (prone to patient errors given speed of titration)

Strong Strategic & Commercial Case for Novel Combination in TRD

Recent success in psychiatry strongly supports combination approach and novel mechanism

	COBENFY™ (xanomeline and trospium chloride) capsules 50mg/20mg, 100mg/20mg, 125mg/30mg	Auvelity™ (dextromethorphan HBr and bupropion HCl) extended-release tablets 45mg/105mg
Innovation	Antagonistic combination to mitigate AEs in schizophrenia (SZ)	Synergistic combination of two generic medications
Clinical Benefit	Novel MoA in SZ with Cohen's D > 0.5	Novel combination in MDD with similar effect size to existing Tx (d=0.35)
Projected/Est. Peak Revenue*	**$3bn - $6bn**	**$1bn - $3bn**

Recent combination analogs demonstrate…

- improved tolerability,
- larger effect size,
- more convenient dosing,
- and novel MoA in disease…

can result in significant adoption by physicians and substantial commercial success

If clinical effects and tolerability profile remain consistent with observed data, we expect ALTO-207, as a novel combination with a differentiated mechanism in depression, has blockbuster potential

**Source: Bloomberg consensus estimates*

Multiple near-term clinical milestones expected

Capitalized through multiple clinical milestones:
Expected cash runway into 2028

2025

- ALTO-203 MDD POC data (2Q 2025)
- ALTO-101 CIAS POC data (2H 2025)

2026

- ALTO-300 Phase 2b MDD data (mid-2026)
- ALTO-100 Phase 2b BPD data (2H 2026)

2027

- ALTO-207 Phase 2b (potentially pivotal*) TRD data

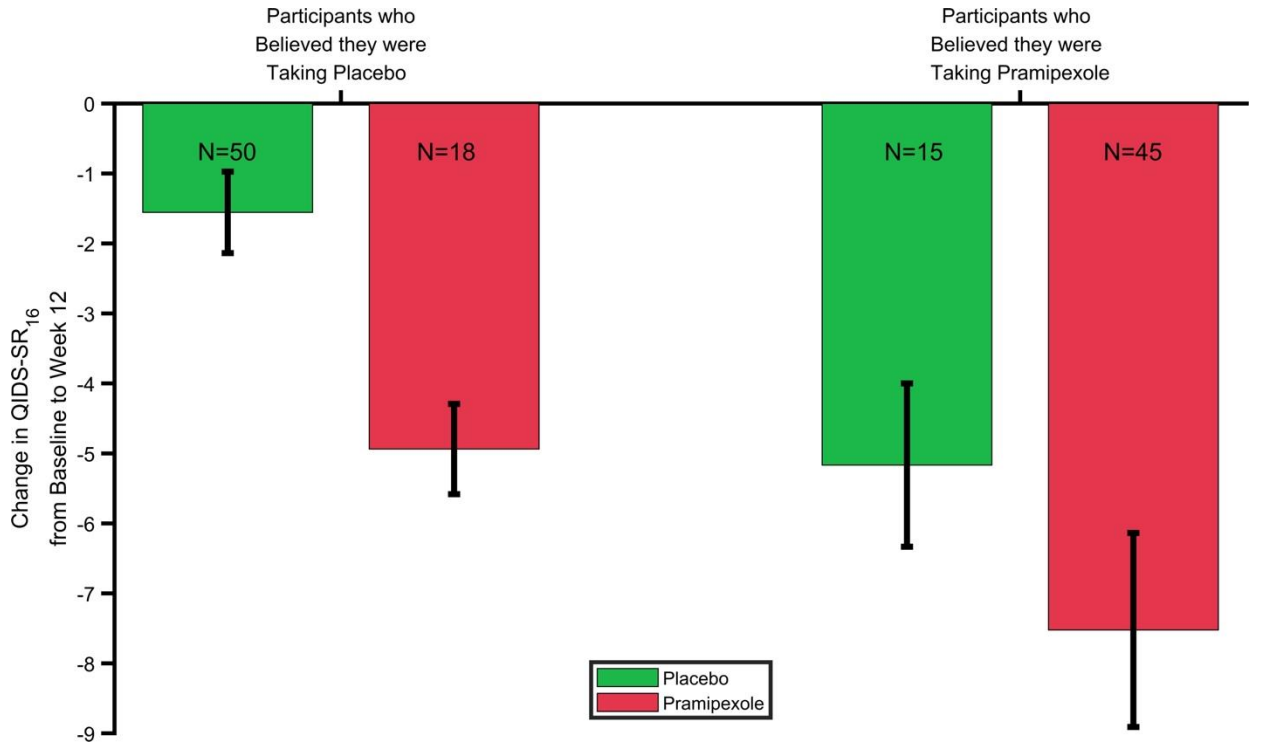
Study qualifying as pivotal is subject to FDA feedback and review of data

Q&A

Appendix

Pramipexole's striking clinical effect, not AEs, led patients to guess arm simply based on whether they improved

- 75% of patients correctly guessed their arm
- Was related to clinical effect – generally noted pramipexole if felt better, placebo if did not
- **Treatment effect was significant in patients who thought they got placebo (p=0.005)**
- Treatment effect remained significant in overall sample even when accounting for guessed arm



Browning, under review