

# ALTO NEUROSCIENCE

**NYSE:** ANRO — November 2026

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# 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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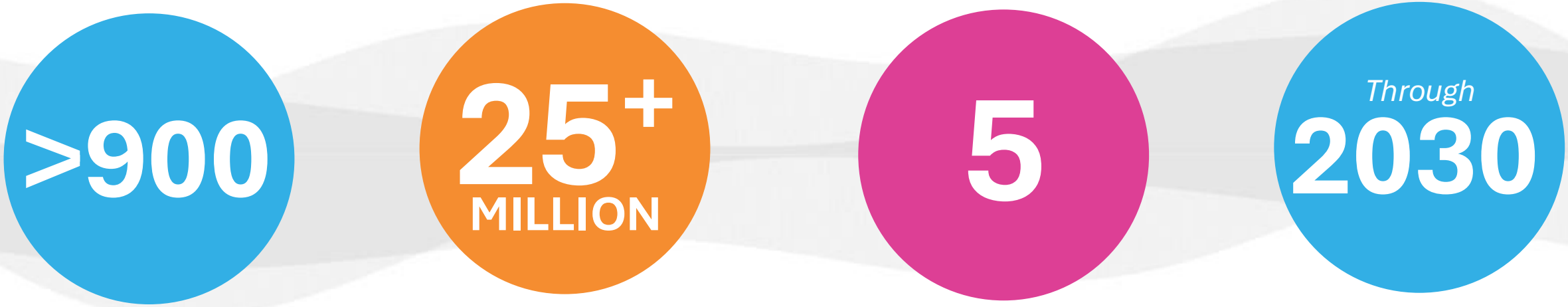
# Alto by the numbers

**Advancing**
a leading, clinical-stage precision medicine portfolio for the brain




**Patients Dosed**
Across studies with Alto's novel product candidates and precision approach

**Patient Impact**
Opportunity across the portfolio

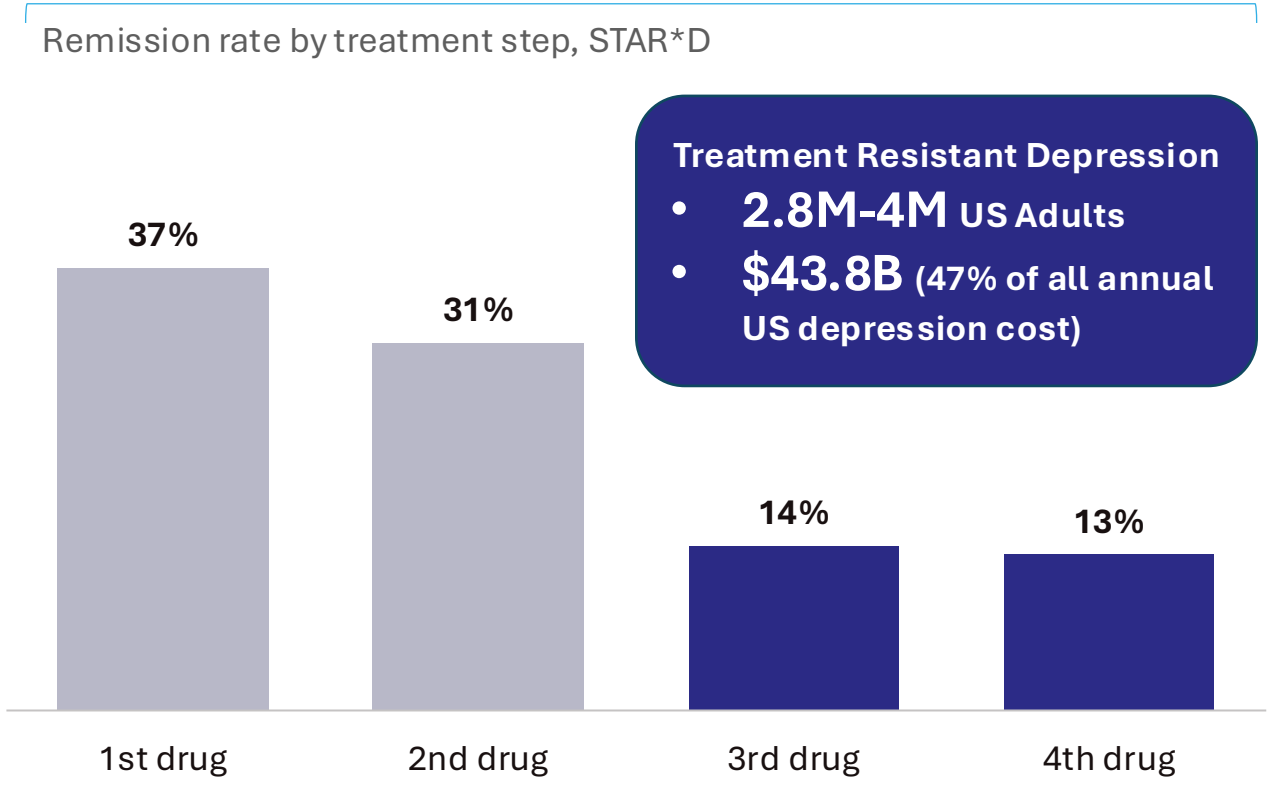
**Late-Stage Data Readouts**
In next ~3 years

Expected **Cash** Runway

# Alto's pipeline addresses major unmet needs across psychiatry

**61.5M US Adults had a mental illness in 2024** – for most, treatment is chosen by trial-and-error and often ineffective

21.4M US Adults with Major Depressive Disorder (MDD; 2024)




## MDD & TRD

Addressed by two programs targeting different mechanisms

**ALTO-207 · Phase 2b topline 2H 2027**

**ALTO-300 · Phase 2b topline 1H 2027**

## Bipolar: 7M

U.S. adults with bipolar disorder, and only treatment for bipolar depression are antipsychotics

**ALTO-100 · Phase 2b topline mid 2027**

TRD: inadequate response to 2+ antidepressants. Sources: SAMHSA, 2024 NSDUH (61.5M, 21.4M); NIMH, NCS-R (bipolar disorder, 2.8% of U.S. adults); Zhdanava et al., J Clin Psychiatry, 2021 (2.8M); Compass Pathways, 2025 (~4M); STAR*D: Rush et al., Am J Psychiatry, 2006

# Robust late-stage pipeline in mental health conditions

***Three PACE studies advance ALTO-207 in treatment-resistant depression, with two additional biomarker-defined Phase 2b readouts expected in 2027***

## Lead program clinical studies




| Candidate (MoA) | Study | Indication & design | Phase 1 | Phase 2 | Phase 3 | Next anticipated milestone |
|---|---|---|---|---|---|---|
| **ALTO-207** (D3/D2 & 5-HT3) | **PACE-1** | **Adjunctive TRD** Ph 2b • n≈178 • 1:1 vs placebo • 8 wks • MADRS • potentially registrational* | | ■ | | **Topline data 2H 2027** |
| | **PACE-2** | **Adjunctive TRD** Ph 3 registrational* | | | ▭ | **Initiation planned early 2027** |
| | **PACE-3** | **Monotherapy TRD** Ph 3 registrational* | | | ▭ | **Initiation planned 2H 2027** |
| **ALTO-300** (MT1/2 & 5-HT2C) | **Ph 2b** | **Major depressive disorder** EEG biomarker-defined | | ■ | | **Topline data 1H 2027** |
| **ALTO-100** (BDNF) | **Ph 2b** | **Bipolar depression** Biomarker-defined | | ■ | | **Topline data mid 2027** |

## Additional clinical-stage candidates

**ALTO-101^**
(PDE4)
Cognitive disorders
Ph. 2 PoC completed

**ALTO-203**
(H3)
Neuropsychiatric disorders
Ph. 2 PoC completed

**ALTO-202**
(NMDA NR2B)
Major depressive disorder
Ph. 2 ready

**ALTO-208**
(D3/D2 & NK-1)
Parkinson's disease
Ph. 2 ready

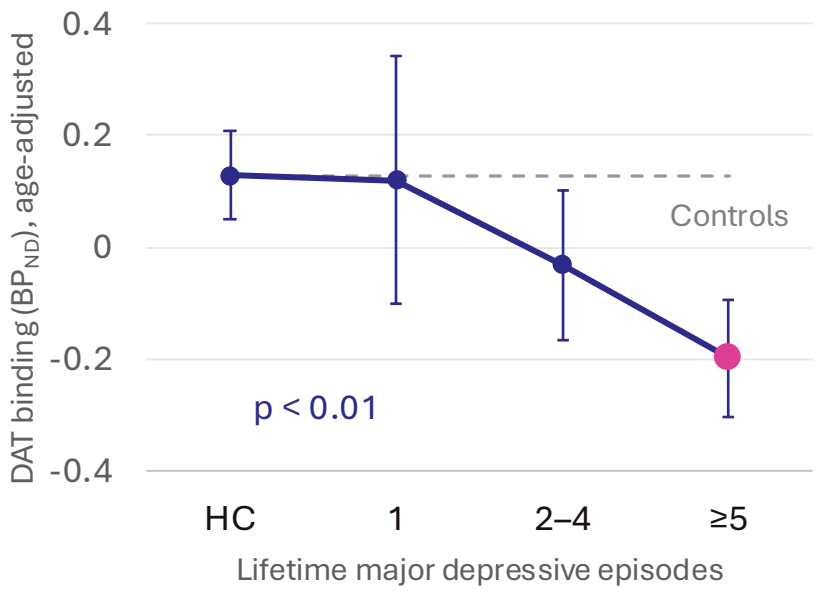
**Registrational intent subject to FDA feedback and review of Phase 2b data. ^Fast Track Designation.*

# ALTO-207

## A potential best-in-disease treatment for TRD

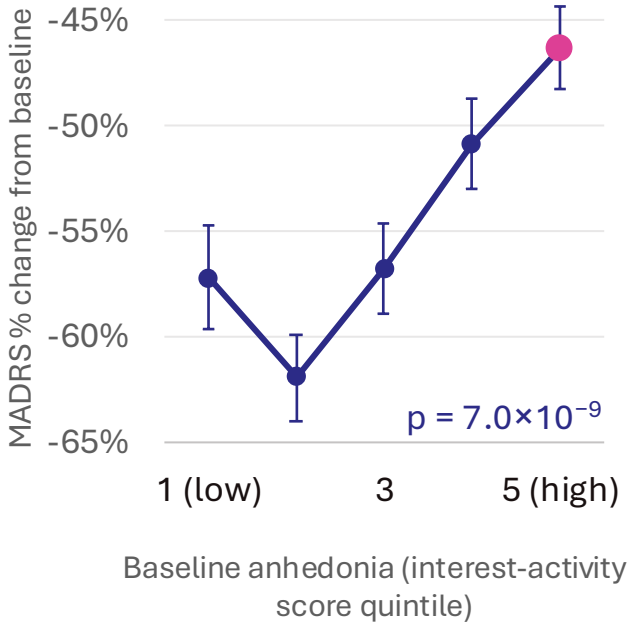
# Low dopamine and anhedonia mark TRD: the core ALTO-207 targets

## Greater dopaminergic dysfunction (by PET) in more resistant patients

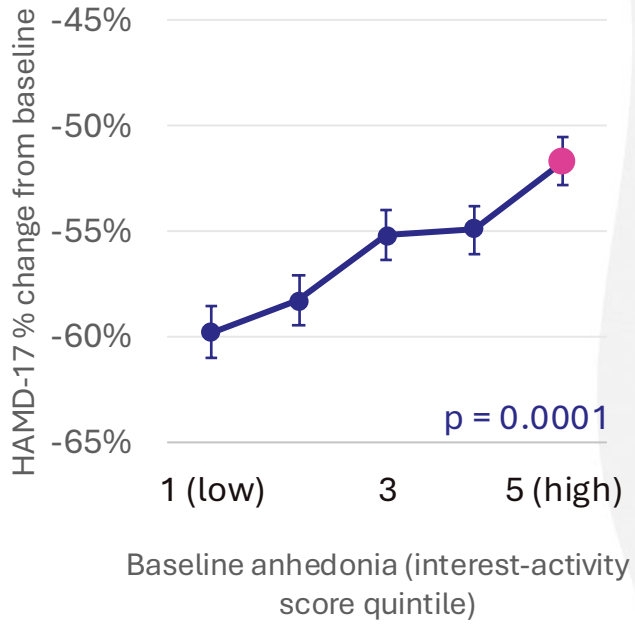



## More anhedonia, weaker antidepressant response

**GENDEP**
Escitalopram or nortriptyline



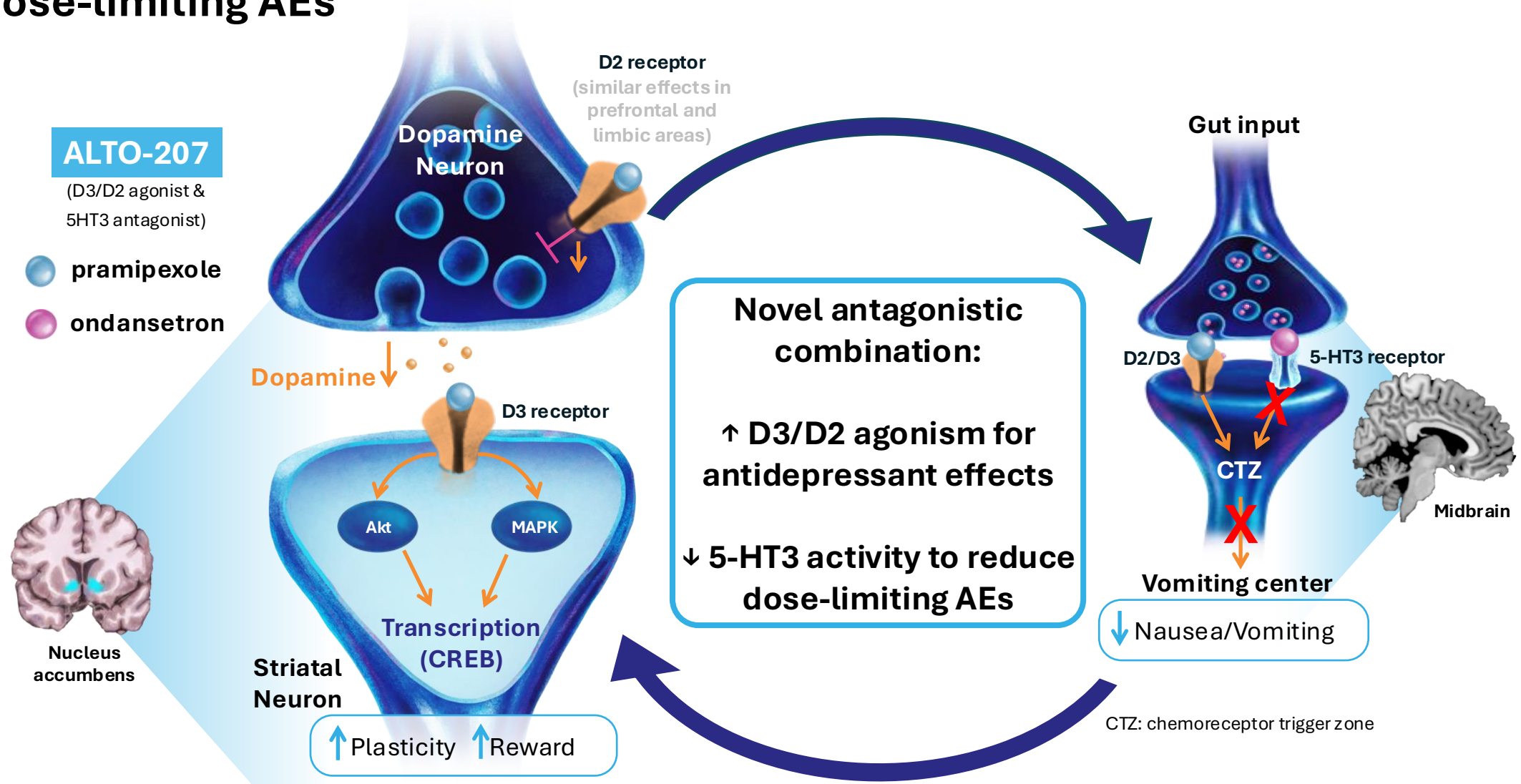

**STAR*D level 1**
Citalopram




**Alto EEG digital twin dopamine signature verified hypodopaminergic TRD phenotype**

DAT (dopamine transporter) PET: Pizzagalli et al., JAMA Psychiatry; GENDEP, STAR*D: Uher et al., Psychol Med, 2012

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



# ALTO-207 builds on pramipexole's large antidepressant effect while designed to address the key tolerability barrier

ALTO-207: fixed-dose pramipexole + ondansetron in a modified-release formulation

The opportunity

**Pramipexole works in TRD, but side effects limit its use**

**d = 0.87**

effect size in TRD, PAX-D trial (n=150)

**4×**

more side-effect dropouts than placebo (20% vs. 5%)

What ALTO-207 changes

**Ondansetron reduces nausea & vomiting, so patients reach effective doses fast**

**d = 1.1**

Phase 2a effect size vs. placebo

**4.1 mg**

mean daily dose in Phase 2a

**5×**

faster titration vs. pramipexole alone

PACE clinical program designed to elucidate strong value proposition across broad TRD patient population

**PACE-1**
Phase 2b, adjunctive TRD
Ongoing - Topline 2H 2027*

**PACE-2**
Phase 3, adjunctive TRD
Planned initiation early '27

**PACE-3**
Phase 3, monotherapy TRD
Planned initiation 2H 2027

**PACE-OL**
Open-label extension
Planned initiation early '27

**Potentially registrational; subject to FDA feedback and data review. Study initiation timing subject to FDA agreement on study design/plan*
*Sources: Browning et al., Lancet Psychiatry, 2025 (PAX-D); Chase Therapeutics Phase 2a of ALTO-207 (CTC-501, n=32, adjunctive MDD).*

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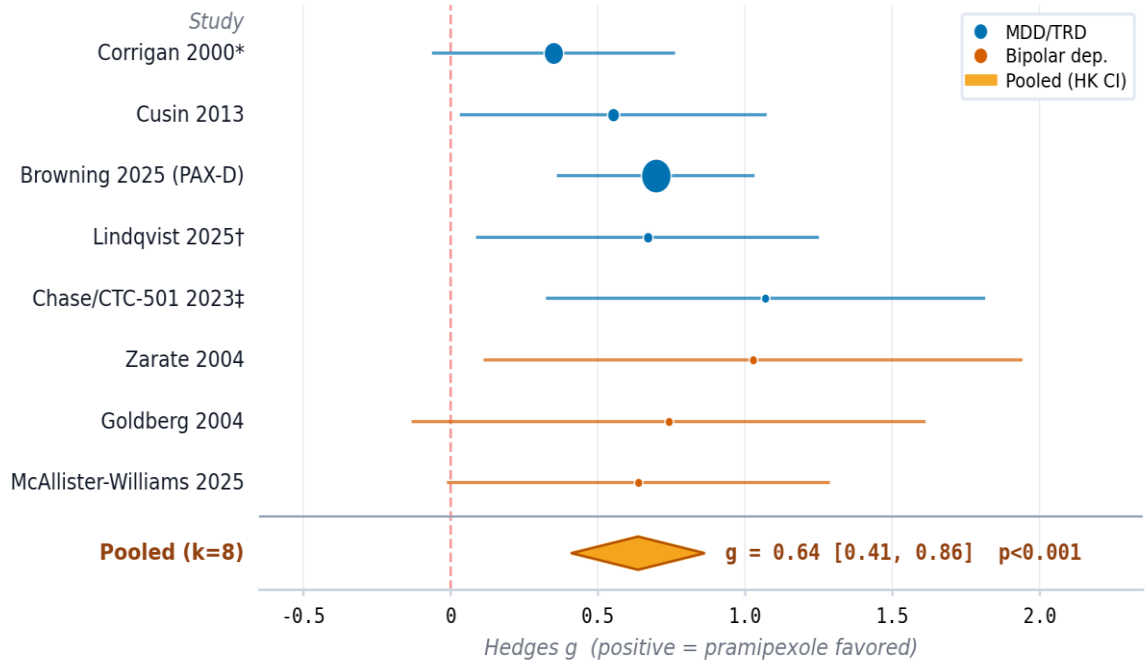
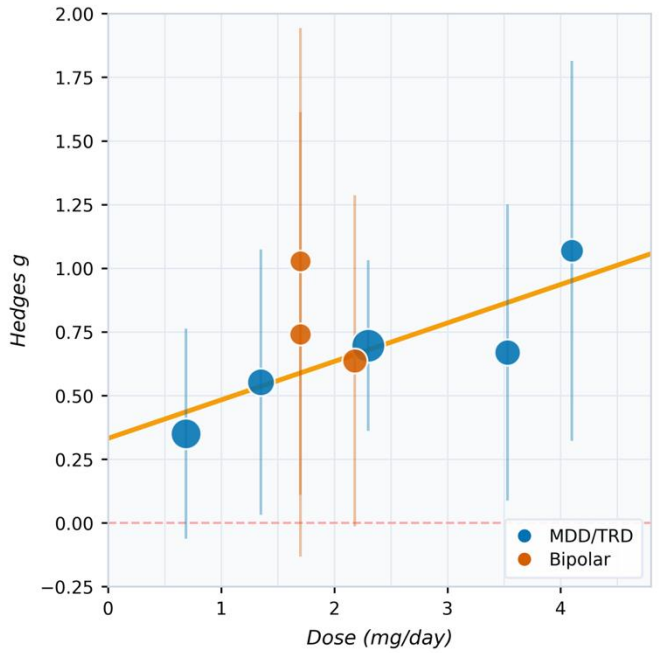
# Across nearly 500 patients, pramipexole's antidepressant effect is consistent and dose dependent

Pramipexole vs. placebo by study, Hedges' g




**Pooled effect: g = 0.64 across 8 studies (p<0.001)**

Effect size by dose, mg/day




**Higher doses, larger effects (p=0.027)**

**Why ALTO-207?**

Ondansetron curbs nausea, so patients reach higher doses: 4.1 mg/day in the Phase 2a vs. 2.08 mg in prior studies

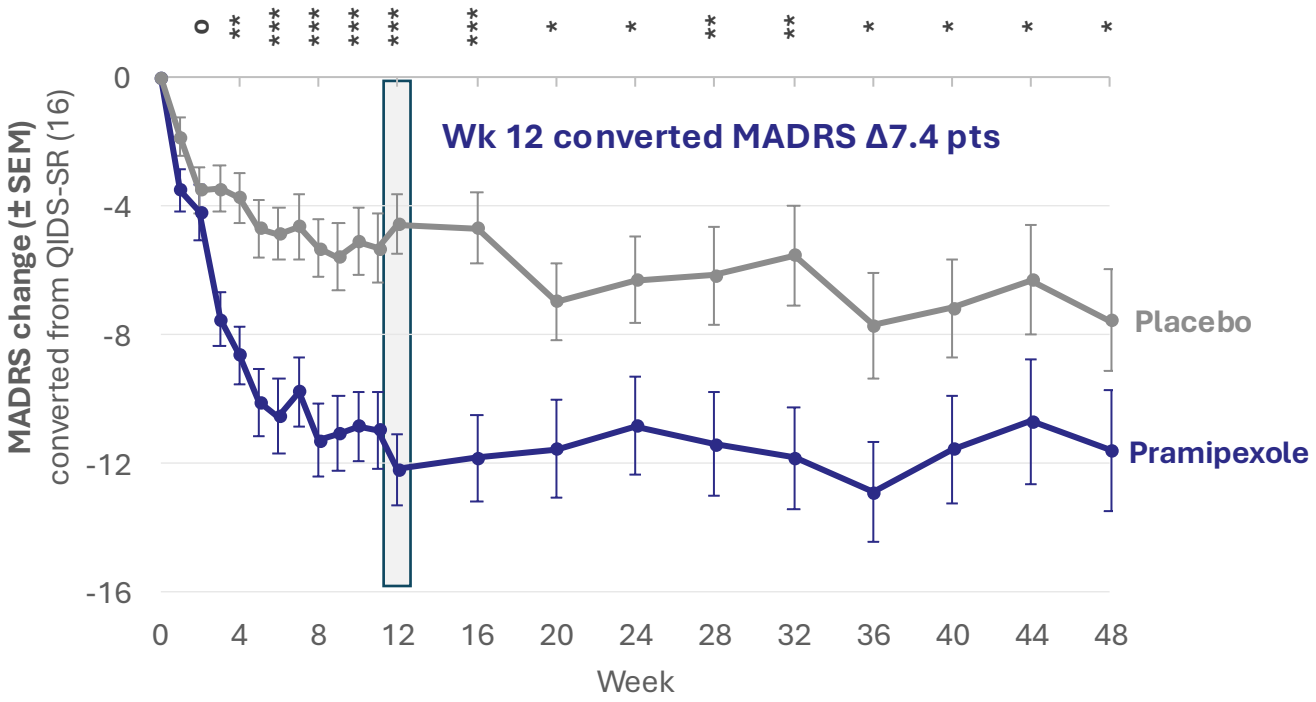
View interactive results ›

Source: Alto meta-analysis of pramipexole trials in mood disorders (MDD, TRD and bipolar depression). Interactive results

# Pramipexole's effect in TRD (d=0.87 in PAX-D) is about 3× that of approved treatments

**PAX-D TRD study (n=150), change in depression score vs. placebo**

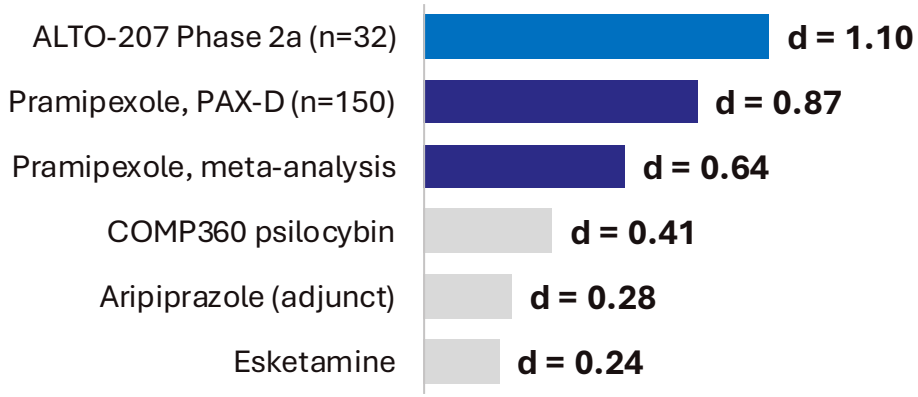
Converted at each timepoint from QIDS-SR to MADRS and re-analyzed




*Adapted from Browning et al., Lancet Psychiatry, 2025*

**Clinical effect of pramipexole stands out**

Effect size, Cohen's d (drug – placebo)




**PAX-D studied a strikingly more resistant population**

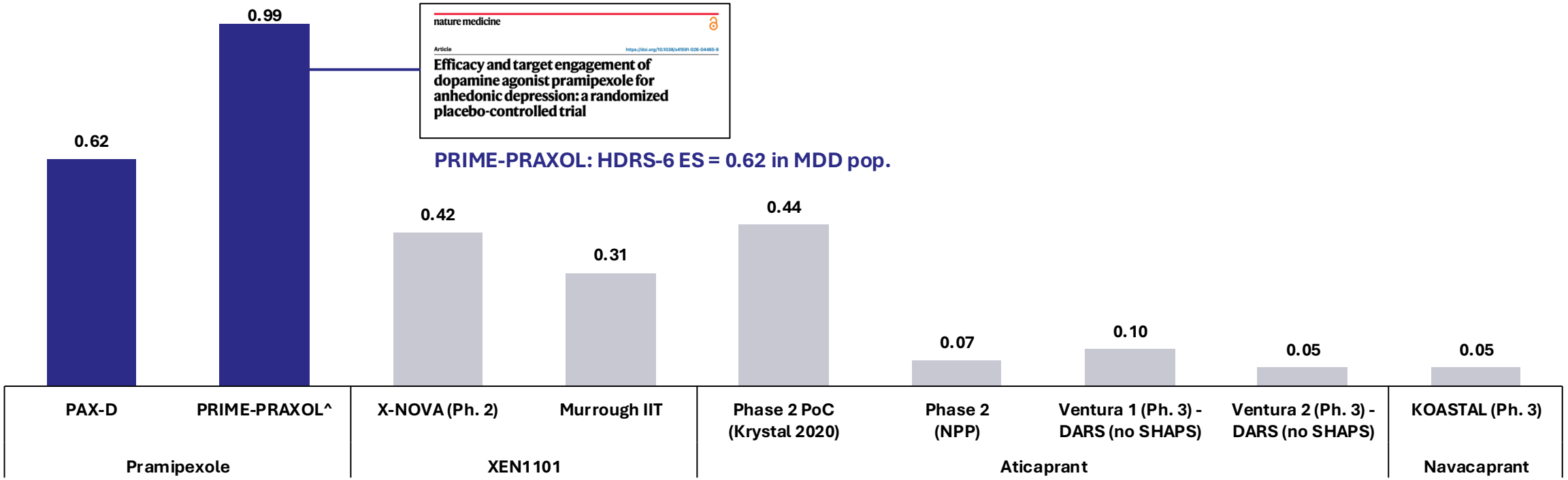
| | % 2 Failures | Episode Duration |
|---|---|---|
| **Esketamine Phase 3** | 61% | 4.5 years |
| **COMP360 Phase 3** | 69% | 3.3 years |
| **PAX-D** | **29%** | **8.5 years** |

Note: PAX-D's 16.4% wk 12 placebo response rate is in line with expectations of 21.9% from meta-analyses in less resistant samples (*Jones et al., JAMA Net Open, 2021*)

*Clinical significance is typically cited at d=0.25–0.3. Note: Effect sizes esketamine and aripiprazole from 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). Effect size from the two COMP360 Phase 3 studies estimated from available information*. QIDS-SR to MADRS conversion *Carmody et al., J Aff Dis, 2006*. Esketamine and COMP360 % failures and episode duration derived from *Salahudeen et al. Ther Adv Drug Saf, 2020; Janik et al, JAMA Psych, 2025*; and Compass Pathways company presentations. The results 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.

# Pramipexole has exhibited field-leading effects on anhedonia, demonstrating potential to address a critical unmet need in depression

**Effect size on anhedonia vs. placebo** Cohen's d, SHAPS unless noted




nature medicine

Article

Efficacy and target engagement of dopamine agonist pramipexole for anhedonic depression: a randomized placebo-controlled trial

**PRIME-PRAXOL: HDRS-6 ES = 0.62 in MDD pop.**

**Clear & consistent effects on anhedonia provide strong differentiation and support for ALTO-207**

^MDD subpopulation, SHAPS effect size. Not head-to-head trials; study designs and protocols differed, and results may not be comparable. Sources: Browning M. et al., Lancet Psychiatry (2025); Ventorp, F. et al. Nature Medicine (2026); Butterfield N. N. et al., JAMA Netw Open (2025) — azetukalner, KV7 opener in MDD.; Fremont et al. ASCP poster 2025; Krystal A. D. et al., Nat Med (2020), Schmidt M E et al., Neuropsychopharmacology (2024); Popova et al. 2025 ASCP Ventura-1/2 Poster; company reports

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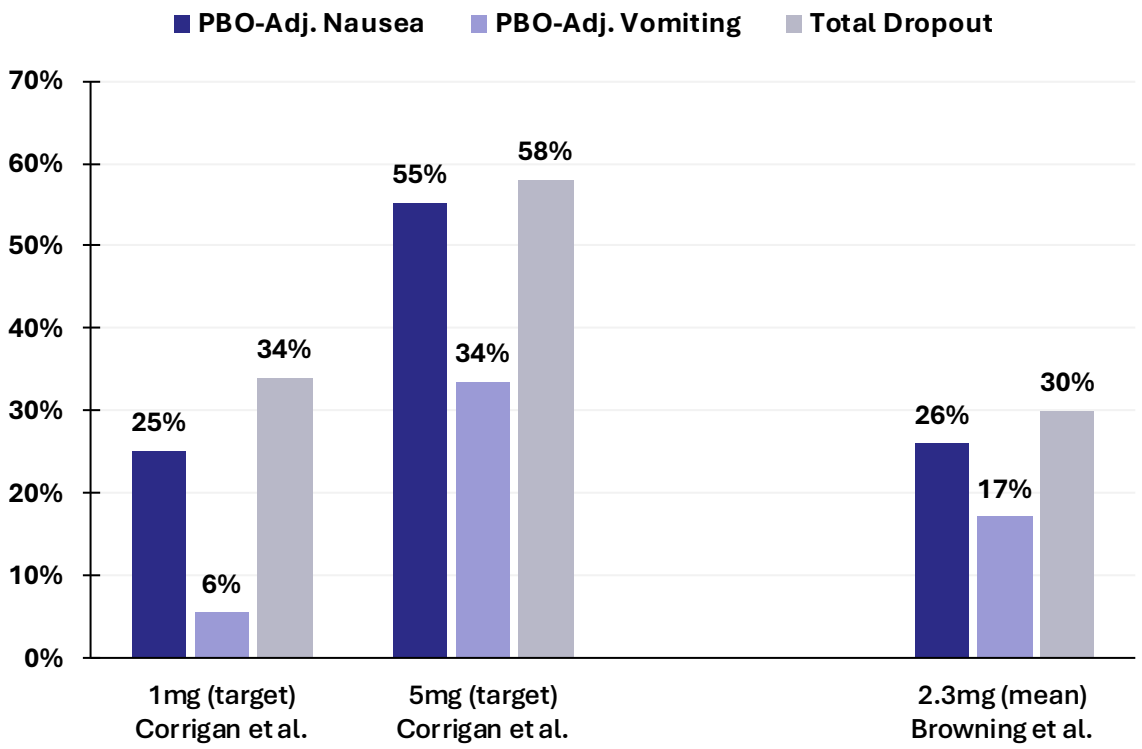
# Nausea keeps real-world pramipexole doses at 0.71 mg, a third of the 2.3 mg dose in PAX-D which showed large effects

**Side effects and dropout by pramipexole dose**

% of patients; nausea and vomiting above placebo




**Real-world prescribing, AllofUs EMR data (N=633,547)**

Patients with MDD taking pramipexole

**658 days**

to reach 1 mg in practice, vs. about 3 weeks on the label schedule

**0.71 mg**

average maximum daily dose → substantially below most efficacious doses

**78%** titrate slower than the label; **16%** need a dose cut within 14 days of increasing it

**ALTO-207 Phase 2a**

**4.1 mg/day** reached in 8 days

Real-world data: only patients with >1 dose level included (single-dose averages 0.24 mg MDD, 0.5 mg Parkinson's). Label schedule per Mirapex prescribing information. Sources: Corrigan et al., Depress Anxiety, 2000 (n=174, MDD, 8 weeks); Browning et al., Lancet Psychiatry, 2025 (PAX-D); Chase Therapeutics Phase 2a (CTC-501, n=32).

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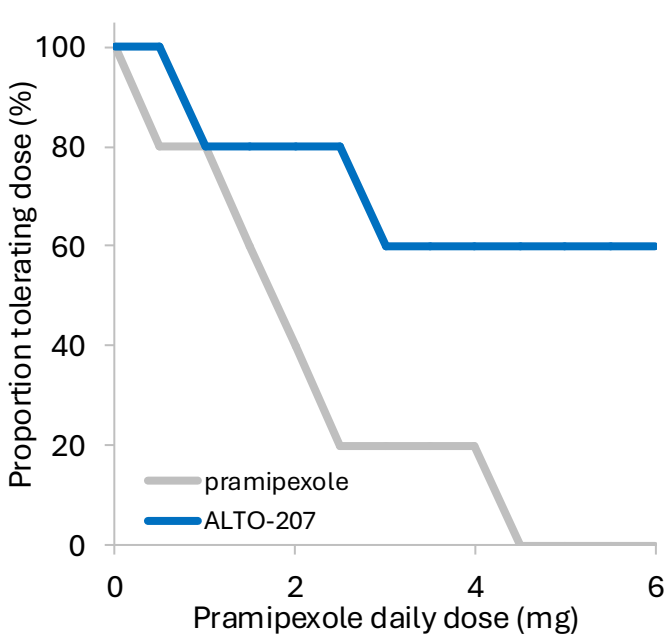
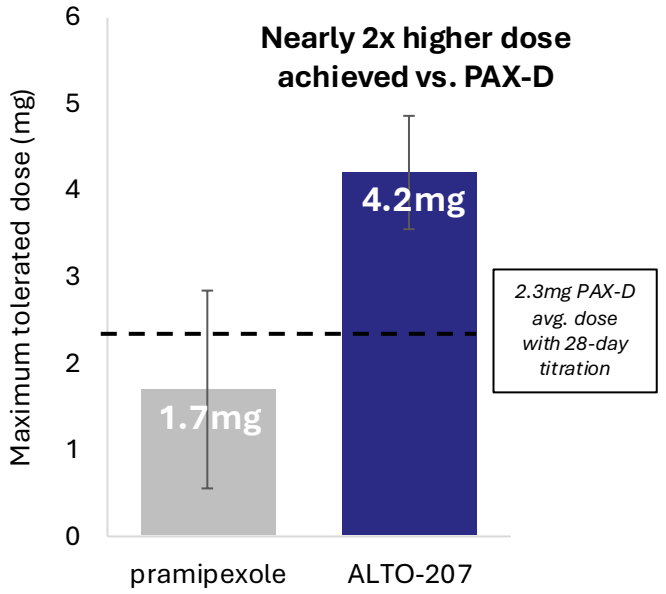
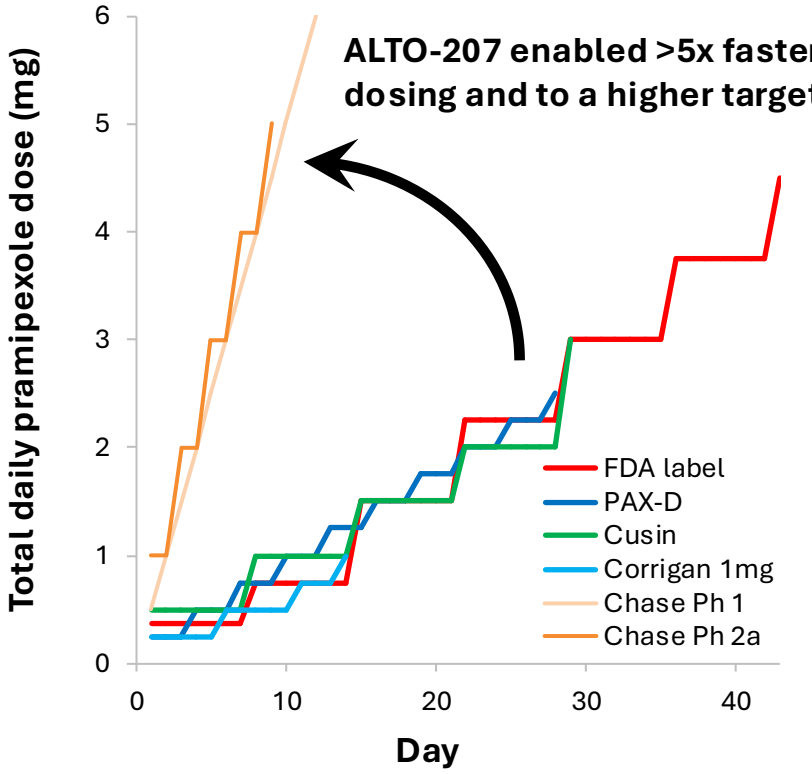
# ALTO-207 combination approach achieved higher pramipexole doses faster and more consistently

## ≥2.5x increase in pramipexole tolerability*




## Until ALTO-207, all pramipexole depression trials followed the FDA-approved titration schedule




- Achieved a **≥2.5-fold higher** max dose vs. pramipexole alone, titrated at 5x the FDA-approved schedule for pramipexole
- **60% of patients tolerated max dose of ALTO-207** (6mg pramipexole), in 12 days

*Chase Therapeutics sponsored trial

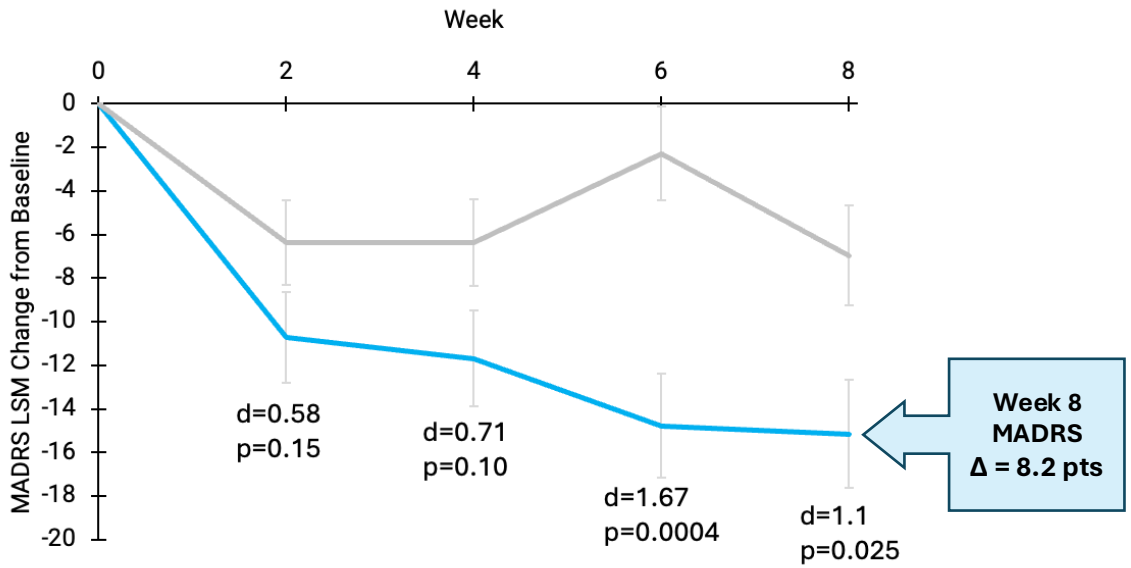
# ALTO-207 Phase 2a results are consistent with the robust antidepressant effects reported for pramipexole in the literature, with improved tolerability

**Phase 2a: MDD randomized, placebo-controlled trial (N=32)***

- Rapid titration to avg of 4.1mg/d pramipexole in 8 days (together with 16mg ondansetron) – 5x faster than pramipexole label
- Moderate-severe MDD (baseline MADRS ALTO-207: 28.8; placebo: 28.2)

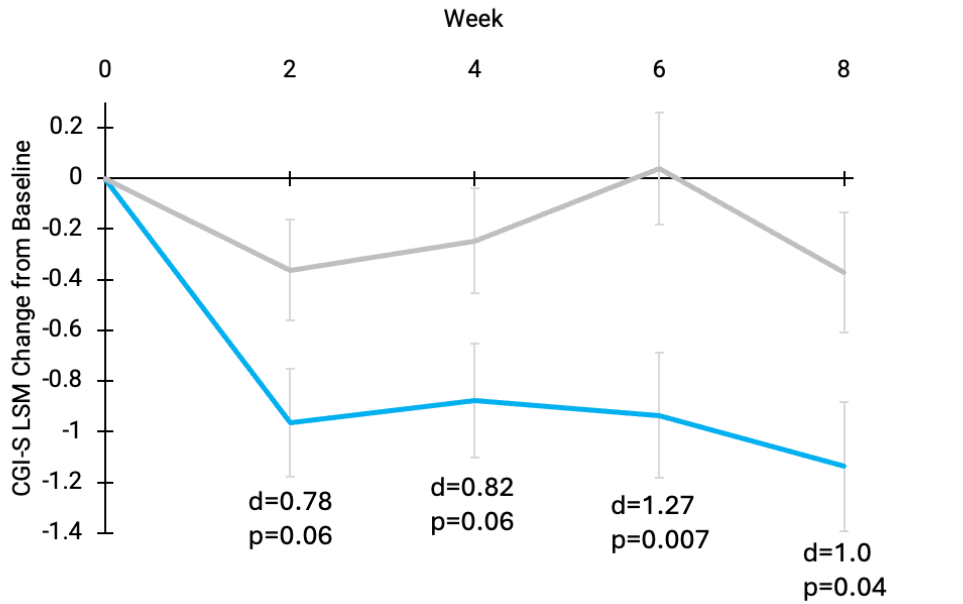
## 1 ALTO-207 demonstrated significantly greater reduction in depressive symptoms compared to placebo

**MADRS – Change from Baseline**




## 2 ALTO-207 demonstrated significantly greater reduction in illness severity compared to placebo

**CGI-S – Change from Baseline**




*Chase Therapeutics sponsored trial

ALTO-207 (n=16)
Placebo (n=16)

ALTO-207 (n=16)
Placebo (n=16)

# Phase 2a trial of 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***

| | **ALTO-207** (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

# The PACE program: a broad development program designed to establish *ALTO-207 as the first-choice treatment for TRD patients*

**PACE:** Pramipexole-ondansetron Assessment of Clinical Efficacy in depression

## PACE-1

**Phase 2b • Adjunctive**

Adjunctive treatment in adults with TRD

N = 178 | randomized 1:1 vs. placebo, double-blind; design mirrors PAX-D

**Enrolling • Topline 2H 2027**

## PACE-2

**Phase 3 • Adjunctive**

Adjunctive treatment in adults with TRD

N ≈ 350 | two fixed-dose arms vs. placebo^
- Proposing 1.6mg/15mg & 3.2mg/15mg dose arms vs. placebo with titration schedule aligned with PACE-1

**Planned • Initiation early '27***

## PACE-3

**Phase 3 • Monotherapy**

Monotherapy treatment in adults with TRD

**Planned • Initiation 2H 2027***

## PACE-OL

**Open-label Extension**

Long-term safety and durability in patients completing PACE-1, PACE-2 or PACE-3

**Planned • Initiation early '27***

### Common design elements across the program

**Population**

Adults with TRD (2–5 prior treatment failures)

**Primary efficacy endpoint**

Change in MADRS from baseline, with centralized ratings

**Dosing scheme**

Short titration period to target dose, consistent across efficacy studies

**Regulatory pathway**

505(b)(2); program designed to support a broad TRD/Adj. MDD NDA submission

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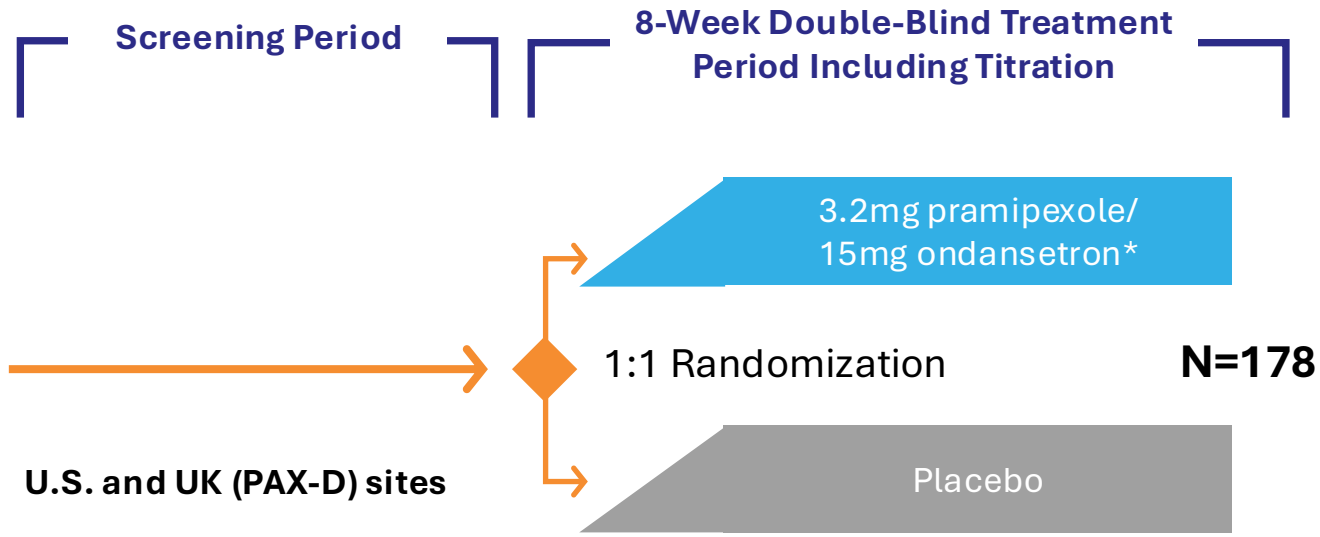
*TRD = treatment-resistant depression; MADRS = Montgomery–Åsberg Depression Rating Scale; NDA = New Drug Application; *Study initiation timing subject to FDA agreement on study design/plan*
*^Study design subject to change following planned FDA interaction*

# ALTO-207 Phase 2b design – topline data 2H 2027

***Adjunctive to an existing antidepressant*** with an insufficient response, mirroring PAX-D

**Key inclusion/exclusion criteria:**

- TRD with 2-5 treatment failures
- On stable antidepressants with insufficient response (which continues unchanged)
- No antipsychotics allowed
- MADRS ≥ 25
- Sponsor eligibility review with medical & pharmacy records required, urine antidepressant testing
- Exclude impulse control disorders




PRIMARY OUTCOME: **MADRS change from baseline**

- Total pramipexole **dose selected to optimize efficacy and limit side effects** based on PAX-D, Chase, clinical practice
- **Proprietary modified release formulation** better PK-matches ondansetron (shorter half-life) to pramipexole
- Custom titration schedule to top dose by day 13
- **Starter pack to make titration straightforward** and mirror ultimate commercial approach
- Central raters to reduce variability, with interview monitoring by Alto's proprietary LLM-based MADRS scoring system

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* Total daily dose divided twice daily (BID)

# ALTO-207 is positioned as the first TRD treatment, before Auvelity, antipsychotics, esketamine and psychedelics

**Major depression**

**Treatment-resistant depression (2+ failed antidepressants)**

| 1st antidepressant | 2nd antidepressant | ALTO-207 | Auvelity | Adjunctive antipsychotic | Esketamine | Psychedelics |
|---|---|---|---|---|---|---|
| SSRI or SNRI<br>37% reach remission | Switch or combine class etc.<br>31% reach remission | **Monotherapy**<br>Replaces the AD<br><br>**Adjunctive**<br>Added to the AD | Oral, twice daily<br>MDD label, not TRD-specific | Abilify, Rexulti, Vraylar, Caplyta<br>Weight gain, akathisia | Spravato nasal spray<br>In-clinic, 2-hour monitoring | Psilocybin (COMP360)<br>Under FDA review, in-clinic dosing, significant hallucination/ unblinding |

U.S. adults, depression treated with medication

**8.9M**
take medication for major depression

**2.8M–4M**
have TRD, the population ALTO-207 targets

**<5%**
of TRD patients get an FDA-approved TRD drug today

AD: antidepressant. Auvelity is approved for MDD, not specifically for TRD. Sources: Zhdanava et al., J Clin Psychiatry, 2021 (8.9M, 2.8M TRD); Rush et al., Am J Psychiatry, 2006 (STAR*D remission); Compass Pathways Q4 2025 results (~4M TRD; <5%); Spravato U.S. label, 2025

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# Clinic-based TRD drugs reach fewer than 5% of patients; ALTO-207 is a pill any prescriber can give

~4M U.S. TRD patients



**<5%**

get an FDA-approved TRD drug, mostly Spravato in a clinic

**>95%**

could get an oral pill from the doctor they already see

| | ALTO-207 | Spravato | Psychedelics |
|---|---|---|---|
| **Where it's taken** | At home | Certified clinic | Certified clinic (expected) |
| **Time in clinic per dose** | None | 2+ hours observed | ~6- to 8-hour session |
| **Dosing** | Twice-daily pill | Twice weekly, then weekly or every 2 weeks | 1–2 sessions plus prep and follow-up visits + re-dosing |
| **Who can provide it** | Any prescriber, incl. primary care | ~7,000 certified sites | Certified sites with trained staff |
| **Risk Evaluation Program (REMS)** | **Not expected** | Required | Expected |

Psychedelics: COMP360 psilocybin is in FDA review; delivery is based on trial protocols and the expected REMS.

ALTO-207 is investigational; label and REMS status not yet determined. Sources: Compass Pathways Q4 2025 results (~4M U.S. TRD; <200K, or <5%, get an FDA-approved TRD treatment); Spravato U.S. label and REMS, 2025; Bloomberg, 2026 (7,000+ sites); COMP360 Phase 3 protocols.

ALTO NEUROSCIENCE

# Novel ALTO-207 product attributes and substantial patient risk deters *off-label* generic substitution

## Key attributes of ALTO-207 that mitigate likelihood of generic substitution

- Strong IP portfolio covering formulation, use, and titration protects from generic combination entry
- Simple dosing & titration regimen (starter pack)
- Single pill for ease of administration
- Clear evidence of effect of combined product, if approved
- Commercial strategies can mitigate patient out-of-pocket costs and improve access

## Prescribing off-label generic components introduces substantial patient & prescriber risk

- Complex regimen of generic pills with different timing and half-lives likely to lead to dosing errors & severe adverse events
- Unproven dose levels with non-standard combinations
- Lack of formulation consistency/quality
- Off-label prescribing creates liability for physicians
- Lack of payer coverage for off-label Rx

## Real-world treatment demonstrates lack of generic substitution

**Auvelity (combination of bupropion and dextromethorphan) provides clear evidence that off-label combination generic substitution does not impede significant commercial success**




ALTO NEUROSCIENCE

# New psychiatry drugs have produced $14B acquisitions and are projected blockbusters, the path ALTO-207 is targeting

Recent psychiatry launches and exits

COBENFY (xanomeline and trospium chloride) capsules 50mg/20mg, 100mg/20mg, 125mg/30mg

Karuna → Bristol Myers Squibb

## $14B

acquisition, closed before FDA approval (2024)

**Peak est.: up to ~$5B**

**ALTO-207 link:** New mechanism in a large psychiatric market

CAPLYTA (lumateperone) capsules

Intra-Cellular → J&J

## $14.6B

acquisition post successful launch (2025)

**Peak guidance: $5B (J&J)**

**ALTO-207 link:** Value driven by a depression label, method of treatment IP

Spravato (esketamine) CIII 28 mg nasal spray

Johnson & Johnson

## $1.7B

2025 sales, up 57%, despite in-clinic dosing

**Guidance: $3–3.5B by 2028**

**ALTO-207 link:** Same TRD patient population but with an at-home pill

Auvelity (dextromethorphan HBr and bupropion HCl) extended-release tablets 45mg/105mg

Axsome Therapeutics

## $7.4B

Axsome market cap; Auvelity 2025 sales $507M, +74%

**Peak: ≥$8B, ~$4B in MDD**

**ALTO-207 link:** Novel oral antidepressant, combination product IP

**ALTO-207 combines these ingredients:** a novel mechanism, at-home pill, strong combination and method IP, and a large effect size (pramipexole d = 0.87 in PAX-D) in TRD patients

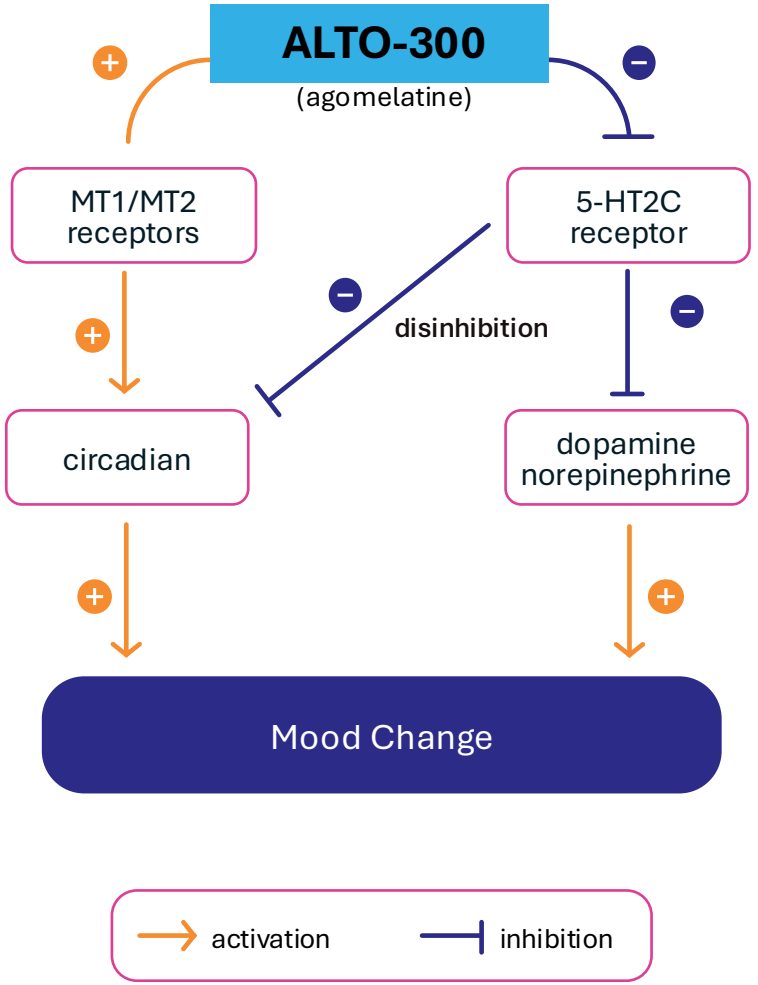
Sources: BMS 10-Q, 2025 (Karuna $14.0B); J&J 10-K, 2025 (Intra-Cellular $14.6B; Spravato $1.7B, +57%); Axsome FY2025 results (Auvelity $507.1M, +74%) and Q1 2026 call (≥$8B peak, split about equally between MDD and Alzheimer's agitation); J&J guidance for Caplyta ($5B peak) and Spravato ($3–3.5B by 2027–28); Cobenfy peak estimates per Bloomberg Sept. 2026; Axsome market cap as of Nov. 10, 2026
ALTO-207 effect size is pramipexole in PAX-D (Browning et al., 2025).

ALTO NEUROSCIENCE

# ALTO-300

## Phase 2b development as adjunctive for MDD

# ALTO-300 proposed mechanism of action: synergy between melatonergic agonism and 5-HT2C antagonism




ALTO-300 is a multi-modal antidepressant with a broad range of **synergistic neurobiological effects** that lead to antidepressant activity and favorable tolerability

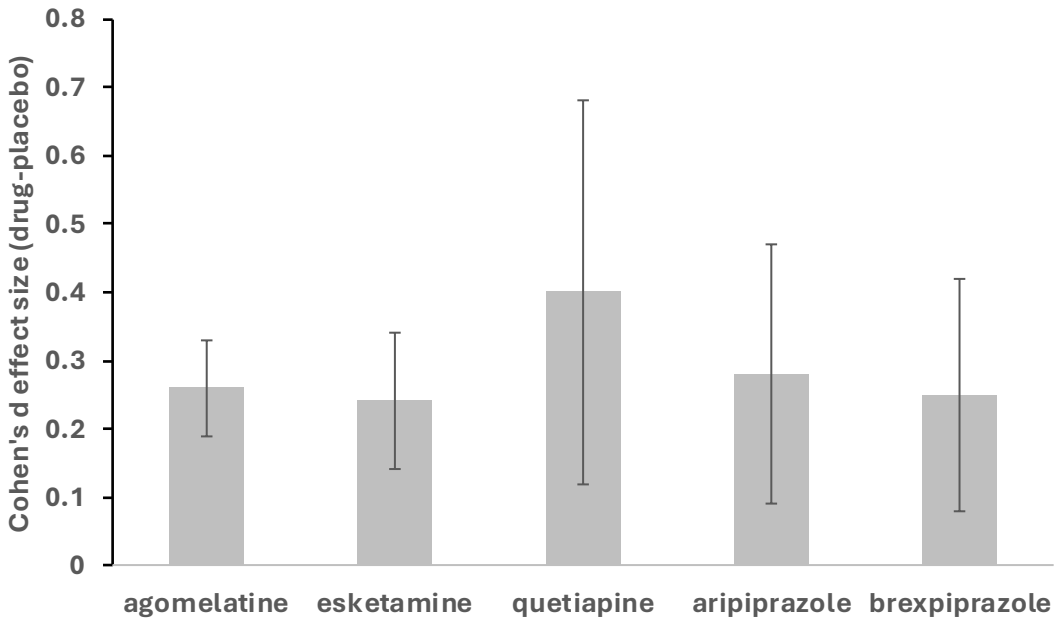
| Antidepressant properties | Melatonergic (MT1 and MT2) Agonism | Serotonergic (5-HT2C) Antagonism |
|---|---|---|
| Enhancement of dopaminergic input to frontal cortex | + | + + |
| Resynchronization of circadian rhythms | + + | + |
| Anxiolysis | + | + |
| Improved sleep quality/patterns | + | + |
| Lack of weight gain and sexual dysfunction | + | + |

*Bodinat et al., Nature Reviews, 2010*

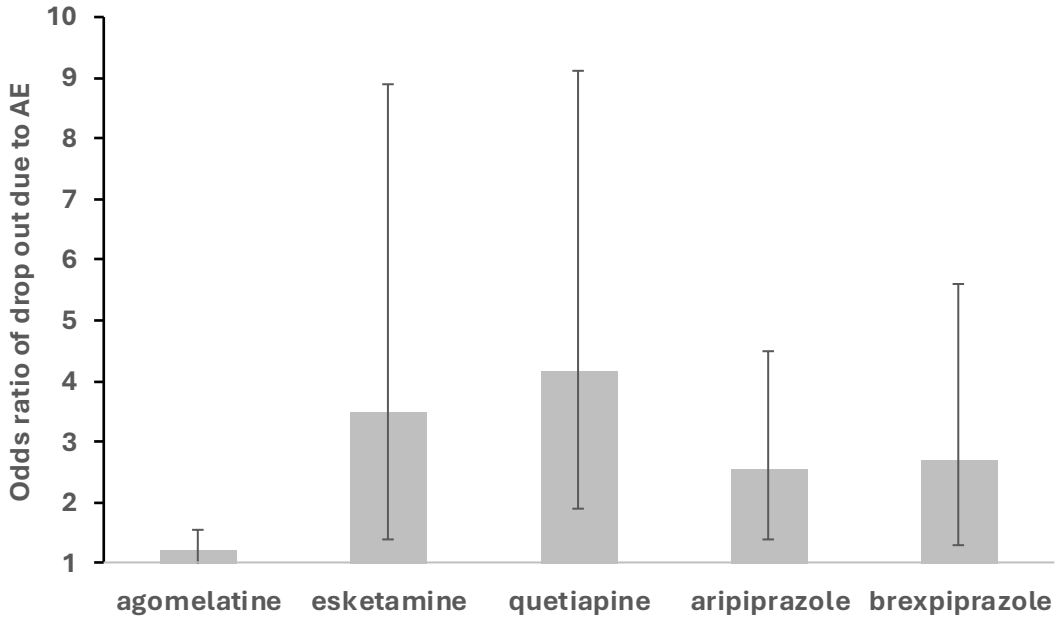
# Unique opportunity for ALTO-300 (agomelatine) as an adjunctive treatment in MDD

## Well-tolerated and validated antidepressant with Ex-U.S. approval (NCE in U.S.) ready for enhancement with a biomarker

**Similar all-comer efficacy as other adjunctive treatments**




**Favorable tolerability compared to other adjunctive treatments**




No difference in dropout due to AE in agomelatine, unlike antipsychotics and esketamine

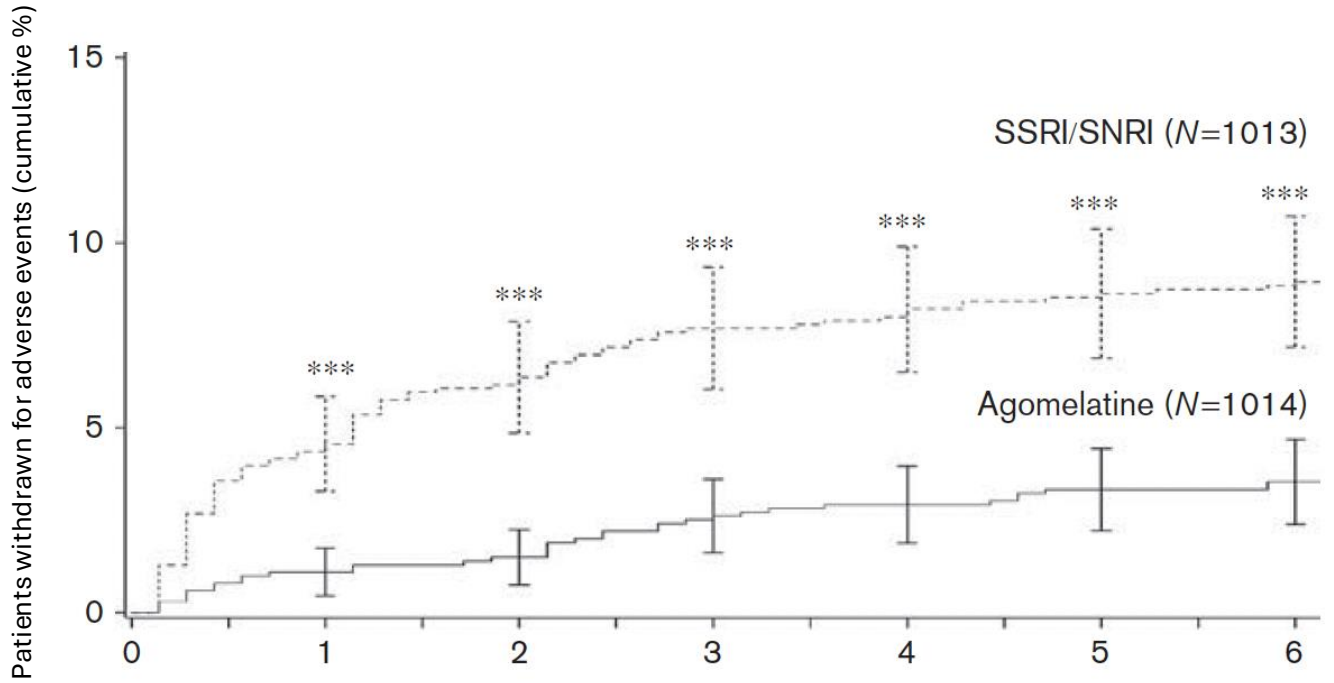
Meta-analytic values drawn from *Cipriani et al., Lancet, 2018; Wang et al., Medicine, 2023; Jawad et al., Exp Op Drug Saf, 2022; Wei et al, JAff Dis, 2020;* Quetiapine, aripiprazole, and brexpiprazole are the atypical antipsychotics approved for MDD.

# Head-to-head clinical trial data positions ALTO-300 favorably even against SSRI/SNRIs, setting up case for adjunctive use

**ALTO-300 (agomelatine): superior efficacy and tolerability**

- Greater efficacy (N=1014) vs SSRI/SNRIs (N=1013) in a pooled analysis on HDRS outcomes: p=0.013 (*Kasper, 2013)*
- Better treatment of anhedonia than venlafaxine XR on SHAPS (Martinotti, 2012)
- Lack of discontinuation symptoms following withdrawal vs. paroxetine *(Montgomery et al., 2004)*
- Fewer sexual side effects than venlafaxine XR *(Kennedy et al., 2008)*

ALTO-300 (agomelatine) consistently better-tolerated with fewer discontinuations versus SSRI/SSNRIs due to adverse events (pooled analysis of randomized trials)




****p<0.001*

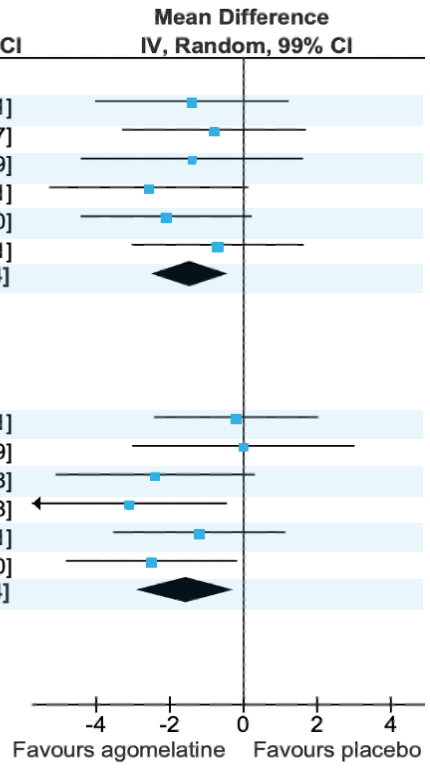
*Kasper et al., International Clinical Psychopharmacology, 2013*

# ALTO-300 at 25mg maintains efficacy while avoiding LFT elevation

## We selected the 25mg dose as meta-analyses show similar efficacy as 50mg

**25mg and 50mg approved in EU/Australia**

| Study or Subgroup | Agomelatine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 99% CI |
|---|---|---|---|---|---|---|---|---|
| **1.11.1 25mg** | | | | | | | | |
| CL3-022 | 14.5 | 8.2 | 129 | 15.9 | 8.6 | 147 | 15.7% | -1.40 [-4.01, 1.21] |
| CL3-023 | 13 | 8 | 141 | 13.8 | 8 | 137 | 17.4% | -0.80 [-3.27, 1.67] |
| CL3-024 | 12 | 8.2 | 148 | 13.4 | 8.4 | 79 | 11.9% | -1.40 [-4.39, 1.59] |
| Loo 2002 | 12.77 | 8.23 | 135 | 15.34 | 8.87 | 136 | 14.9% | -2.57 [-5.25, 0.11] |
| Stahl 2010 | 15 | 8.04 | 158 | 17.1 | 7.92 | 163 | 20.2% | -2.10 [-4.40, 0.20] |
| Zajecka 2010 | 15.9 | 7.74 | 156 | 16.6 | 8.4 | 167 | 19.9% | -0.70 [-3.01, 1.61] |
| **Subtotal (99% CI)** | | | **867** | | | **829** | **100.0%** | **-1.47 [-2.50, -0.44]** |
| Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 5 (P = 0.72); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 3.67 (P = 0.0002) | | | | | | | | |
| **1.11.2 >25mg** | | | | | | | | |
| CAGO2303 | 17.1 | 7.38 | 162 | 17.3 | 7.92 | 158 | 19.2% | -0.20 [-2.41, 2.01] |
| CL3-024 | 13.4 | 8.2 | 147 | 13.4 | 8.4 | 79 | 13.3% | 0.00 [-2.99, 2.99] |
| Kennedy 2006 | 14.1 | 7.7 | 106 | 16.5 | 7.4 | 105 | 15.3% | -2.40 [-5.08, 0.28] |
| Olie 2007 | 13.9 | 7.7 | 116 | 17 | 7.9 | 119 | 15.7% | -3.10 [-5.72, -0.48] |
| Stahl 2010 | 15.9 | 8.25 | 161 | 17.1 | 7.92 | 163 | 18.2% | -1.20 [-3.51, 1.11] |
| Zajecka 2010 | 14.1 | 7.74 | 161 | 16.6 | 8.4 | 167 | 18.3% | -2.50 [-4.80, -0.20] |
| **Subtotal (99% CI)** | | | **853** | | | **791** | **100.0%** | **-1.57 [-2.90, -0.24]** |
| Heterogeneity: Tau² = 0.66; Chi² = 8.54, df = 5 (P = 0.13); I² = 41% | | | | | | | | |
| Test for overall effect: Z = 3.04 (P = 0.002) | | | | | | | | |
| Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0% | | | | | | | | |




*Plot from Koesters et al., Br J Psych, 2013*

### Placebo-like LFT rate for 25mg

- Novartis US studies showed placebo-like LFT rate with 25 mg:
  - **25mg**: 0.3%
  - **Placebo**: 0.3%
  - **50mg**: 3.7%
- Alto's Phase 2a showed no LFT elevation (>3x ULN)
- Even when LFTs increase (mainly 50mg), they are reversible and do not result in liver failure

Agomelatine concerns are more historical/contextual, not clinically meaningful, and less frequent than with antipsychotics (adjunctive MDD comparator drugs)

LFT – Liver Function Test
AST – Aspartate Aminotransferase
ALT – Alanine Transaminase
ULN – Upper Limit of Normal

# Large-scale and real-world use demonstrates agomelatine-induced LFT elevation is low and adaptive

**Acute studies using the 25mg dose (n=4,957) shows placebo-like LFT rate** consistent with Alto's Phase 2a results where no patient exceeded >3x ULN (even with baseline allowance of up to 2x ULN)

**Agomelatine safety supported by low LFT elevation rate following long-term use**

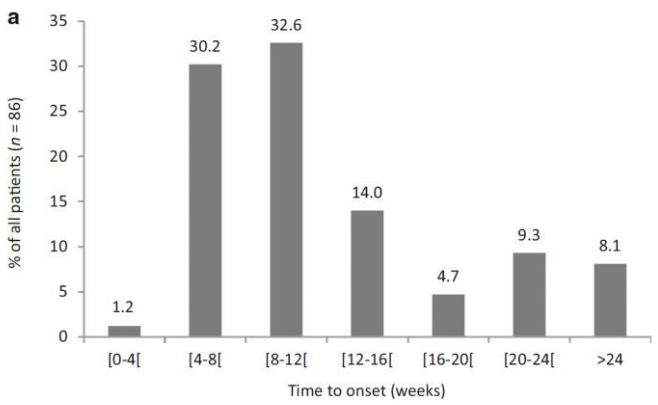
- VIVALDI real-world evidence: Patients (n=3,317) treated with 25-50mg agomelatine over 12 weeks demonstrated very low rates of LFT elevation (~0.2%; *Laux et al., Pharmacopsychiatry, 2012)*

**No difference in the rate of acute liver injury in agomelatine patients (n=74,440) versus conventional SSRI citalopram (n=782,812), following long-term use**

- Even observed a trend in the dataset that suggests less of a risk of acute liver injury with agomelatine vs. citalopram as comparator antidepressant *(Pladevall-Vila et al., CNS drugs, 2019)*

Analysis of patients treated with agomelatine (25 or 50mg/day) demonstrated effects of LFTs are adaptative (n=7,605)

- Onset of LFT elevation at any dose (mainly driven by 50mg) occurred early, before 12 weeks in 64 % of patients and was not cumulative
- Withdrawal of agomelatine led to rapid recovery. The median time to recovery (to ≤2x ULN) was 14 days following treatment withdrawal
- Liver function tests recovered in 36 % of patients despite continuation of agomelatine
- No cases of acute liver failure or fatal outcome occurred




*Perlemuter et al., CNS Drugs, 2016*

## LFT monitoring not expected for ALTO-300 label

LFT monitoring not required for approved antipsychotics despite higher rate of LFT elevation, which is expected to guide the label for ALTO-300

- Approved antipsychotics shown to induce LFT elevation at greater rates (comparable or higher than 50mg agomelatine) and occasionally result in severe or fatal hepatic injury *(Marwick et al., Clin Neuropharm, 2012*)

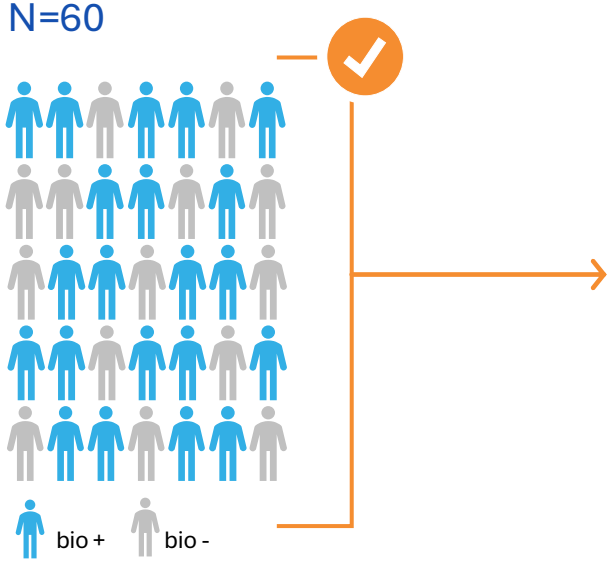
Extensive long-term safety and real-world evidence builds **confidence in lack of liver signal for selected 25mg dose of ALTO-300**

# ALTO-300 Phase 2a: prospective replication of EEG biomarker as predictive of response

**01**

**Determine Biomarker**

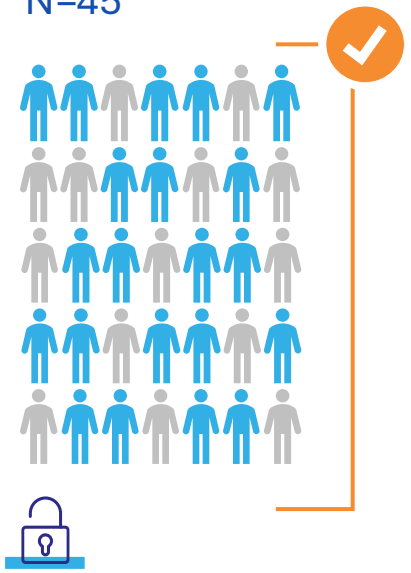
N=60




**02**

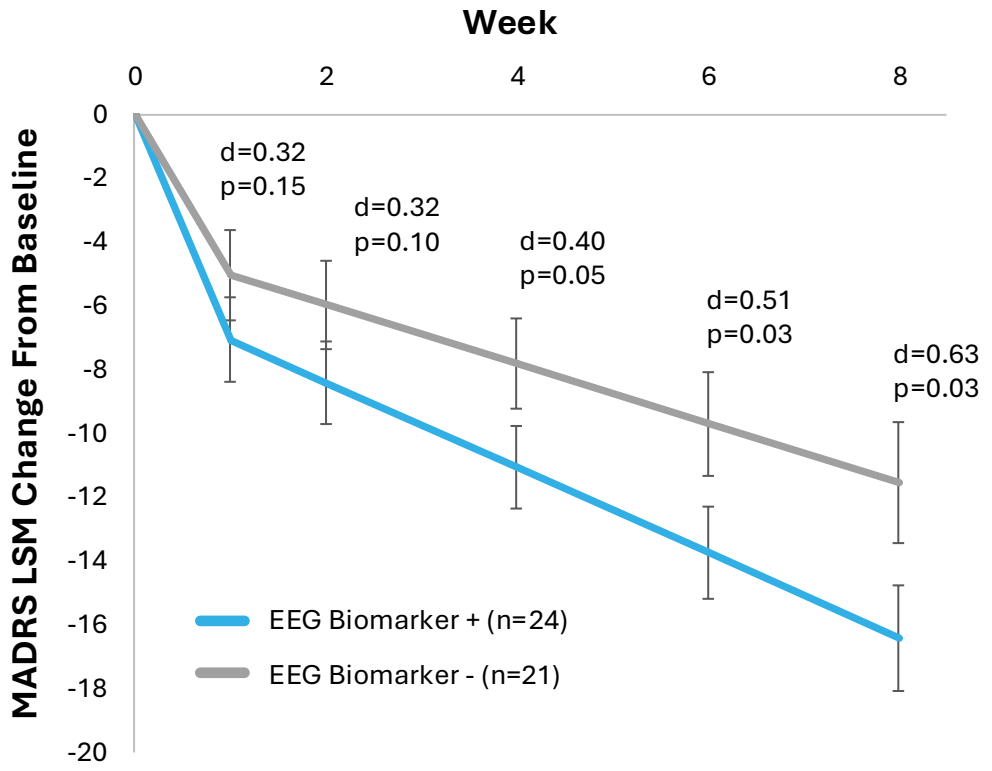
**Prospective Biomarker Validation**

N=45



1. Identified EEG signature as predictive
2. Prospectively label patients as bio+/-
3. Aligned biomarker to drug mechanism of action (rodent and human data)

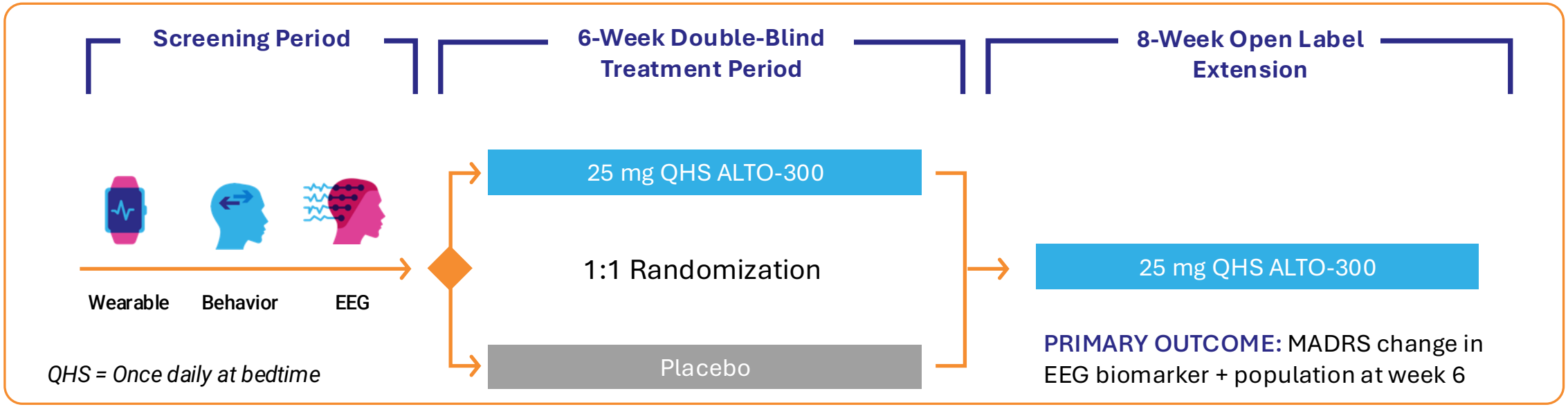
## Prospective Replication in Test Dataset




ALTO NEUROSCIENCE

# ALTO-300 Phase 2b biomarker-guided trial in MDD

Evaluating ALTO-300 as an ***adjunctive to an existing antidepressant*** with an insufficient response

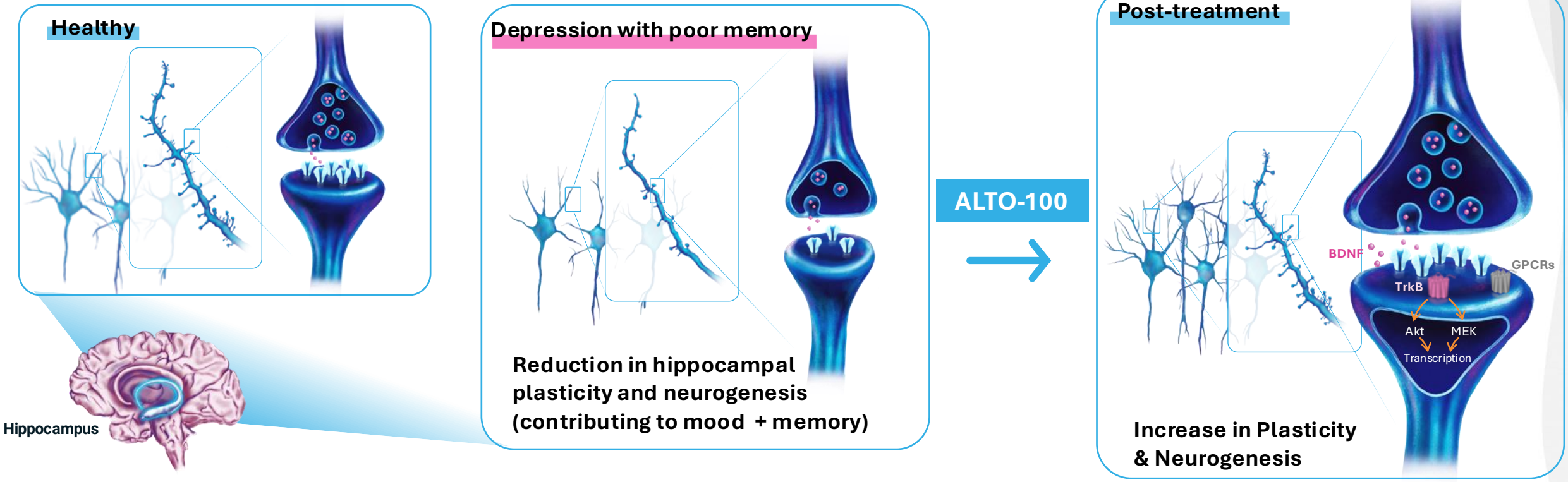



- Design follows **FDA's enrichment guidelines:** powered primary outcome in EEG biomarker positive patients
- **Includes participants with and without the biomarker** and randomization stratified by biomarker status
- Sites and participants blinded to biomarker status
- **Sponsor eligibility review of all participants before randomization**: MGH-CTNI SAFER interview, medical and pharmacy records required along with blood test for underlying mood stabilizer
- **Favorable outcome from interim analysis** informs final sample size; ~200 biomarker positive patients targeted for the final analysis sample to achieve adequate powering

# ALTO-100

## Phase 2b development as adjunctive for bipolar depression

# ALTO-100 offers a novel therapeutic option for depression with poor memory by enhancing hippocampal neuroplasticity

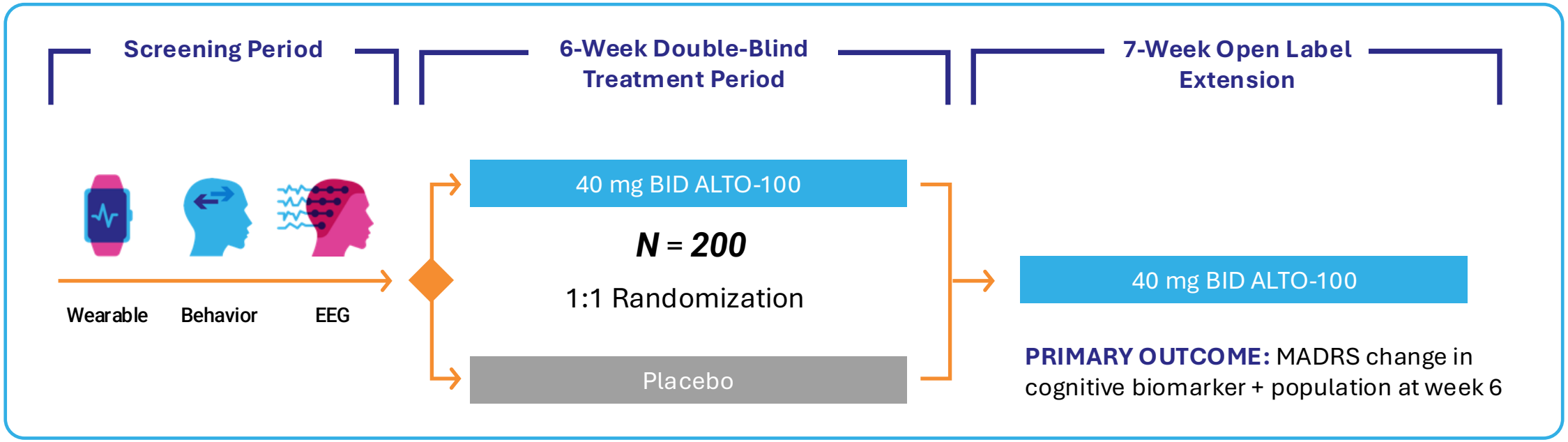



- **Bipolar disorder involves hippocampal neuroplasticity deficits** (like MDD): memory impairment, hippocampal volume decrease, cellular and molecular hippocampal marker reductions (like BDNF) – **ALTO-100 is a hippocampal pro-plasticity intervention**
- **Poor cognition associated with poorer response, greater chronicity/disability** – only available treatments are antipsychotics
- **ALTO-100 MDD Phase 2b demonstrated clinically meaningful signal in adjunctive population**, mirroring bipolar depression study population (adjunctive to mood stabilizers/antipsychotics)

ALTO NEUROSCIENCE

# ALTO-100 Phase 2b biomarker-guided trial in bipolar depression

Evaluating ALTO-100 as an ***adjunctive treatment*** to an existing mood stabilizer/antipsychotic

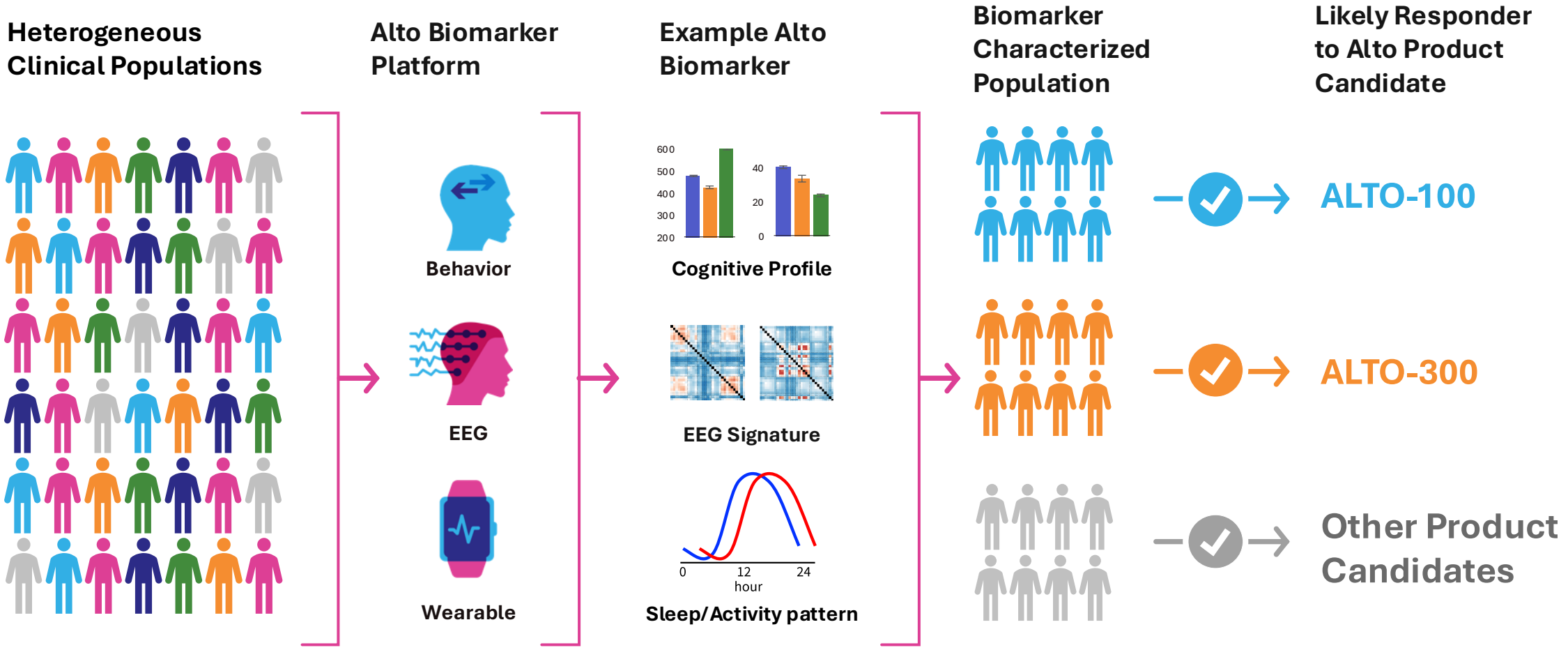



- Design follows **FDA's enrichment guidelines:** powered primary outcome in memory biomarker positive patients
- **Includes participants with and without the biomarker** and randomization stratified by biomarker status (sites, participants and Alto staff blinded to biomarker status)
- **Sponsor eligibility review of all participants before randomization**: MGH-CTNI SAFER interview, medical and pharmacy records required along with blood test for underlying mood stabilizer
- **96% PK positivity** in blinded analysis of 1st cohort – supporting efforts to reduce non-compliance risk

**Study supported by an $11.7mm funding award from Wellcome Trust**

# Platform

# Alto's suite of biomarkers designed to segment patients to drive improved outcomes

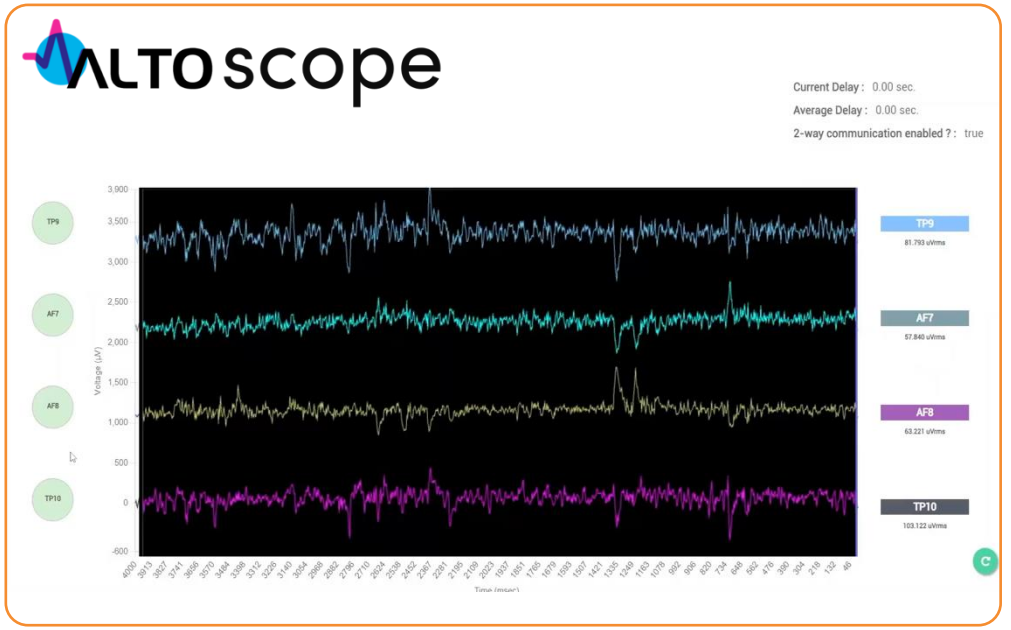


# Leveraging proprietary tools, anticipating commercial scale

## ALTO-100 biomarker is cognitive test-based




## ALTO-300 biomarker is EEG-based



# Multiple near-term clinical milestones expected

Capitalized through multiple clinical milestones:

***Pro forma cash balance of ~$319 as of Sept. 30, 2026 → Expected cash runway through 2030, including ALTO-207 TRD Phase 3 completion & potential NDA submission***

## 2027

- ☐ **ALTO-207 Phase 3 initiation**
- ☐ **ALTO-100 Phase 2b BPD data (Mid 2027)**
- ☐ **ALTO-300 Phase 2b topline data (1H 2027)**
- ☐ **ALTO-207 PACE-1 (Phase 2b, potentially pivotal*) TRD data**

## 2028 - 2030

- ☐ **ALTO-207 Phase 3 TRD readouts & potential NDA filing**

ALTO NEUROSCIENCE

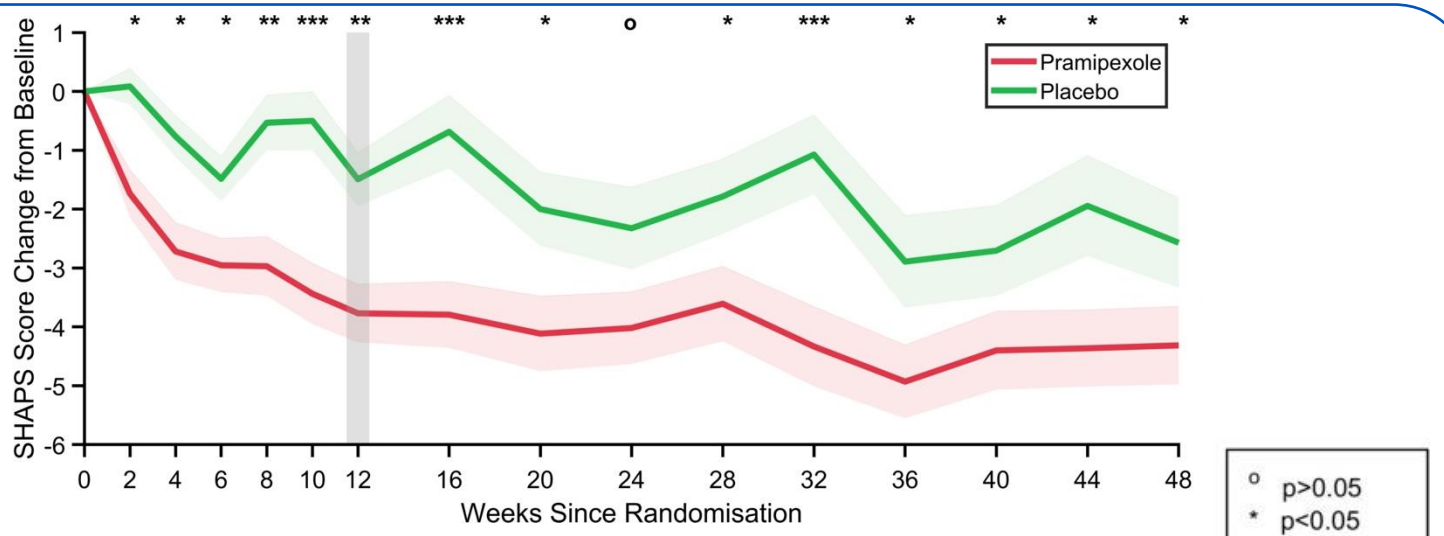
**Study qualifying as pivotal is subject to FDA feedback and review of data*

# Appendix

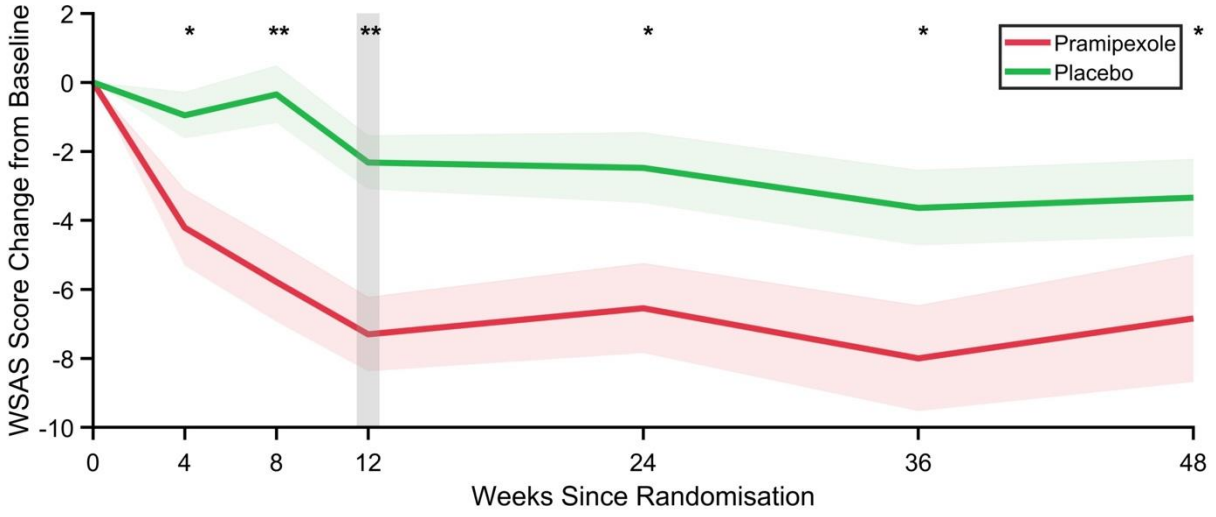
# Additional PAX-D Analyses

# Pramipexole similarly improved anhedonia and functioning

**Anhedonia:** SHAPS




**Functioning:** WSAS

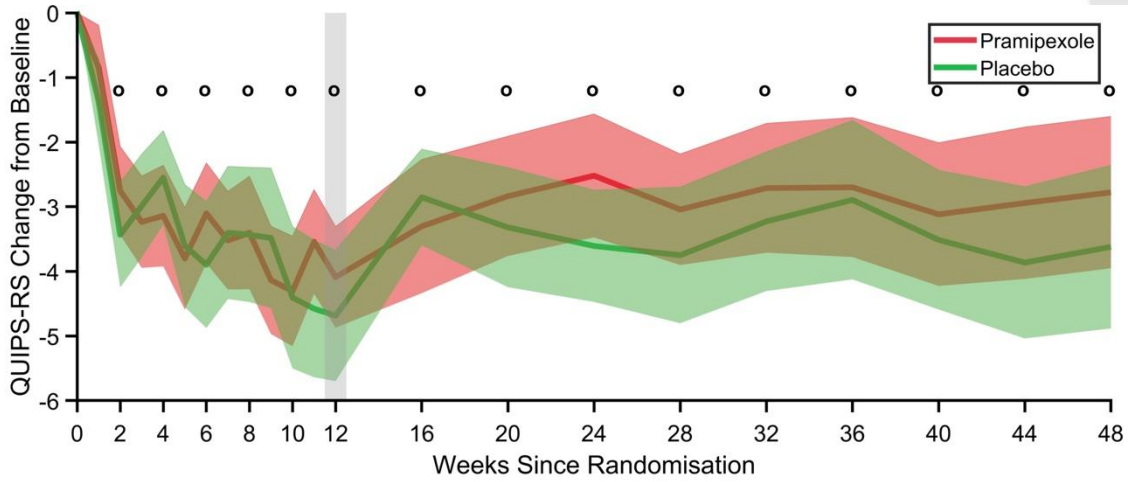



*Suicidality and anxiety similarly improved*

*Browning et. al., The Lancet Psychiatry, July 2025*

# Tolerability: no increase in impulsivity

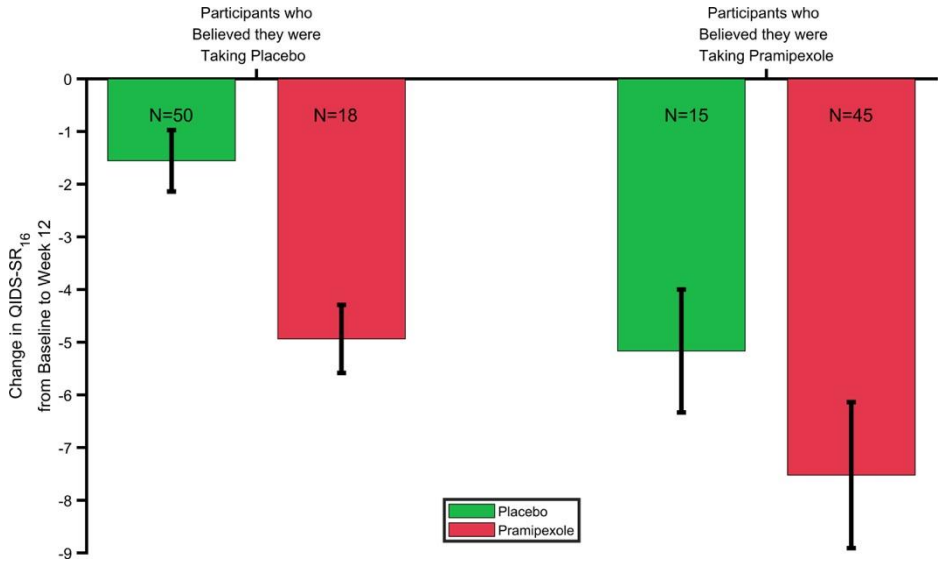
- Reports of increase in impulse control disorders in Parkinson's patients receiving dopamine agonists
- However, this is in the context of a highly perturbed dopaminergic system
- PAX-D data using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIPS-RS) showed 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



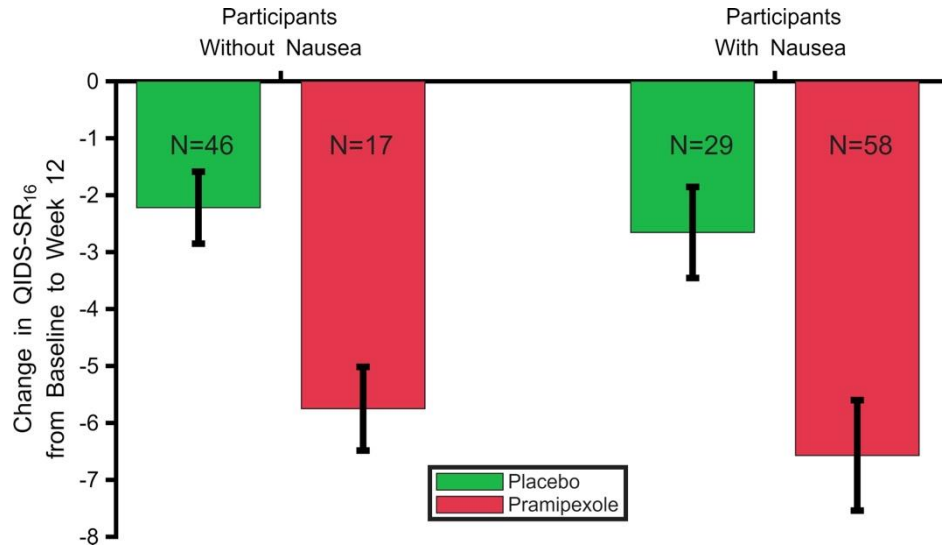

*Browning et. al., The Lancet Psychiatry, July 2025*

# Any unblinding (due to striking efficacy or AEs) does not account for outcome with pramipexole

- PAX-D took the rare step of having patients guess their arm (at 48 wks)
- **Even those that thought they got placebo showed drug superiority (p=0.005)**
- Treatment effect remained significant in overall sample even when accounting for guessed arm




- **Presence of nausea did not impact drug efficacy**
- Nausea did not increase likelihood of correct arm guessing
- Treatment effect unchanged in overall sample even when accounting for nausea
- Similar pattern for other AEs




*Browning et. al., The Lancet Psychiatry, July 2025*

# Impulse control issues with pramipexole are specific to Parkinson's Disease, not depression

**PARKINSON'S DISEASE**

## 17.7%

***Requires stopping the drug***

- 17.7% Impulse-control disorder on pramipexole, n=3,090[1]
- 46% cumulative incidence at five years[2]
- Tapering or stopping the agonist is the only effective treatment; about half resolve at one year, ~19% develop a withdrawal syndrome[2,3]

**DEPRESSION**

## 0–0.7%

***Managed by lowering the dose***

- **Trials:** 2 of 278 (0.7%), both in PAX-D, both resolved on dose reduction; no QUIP-RS separation from placebo[4–8]
- **Registery:** 28 of 18,732 (0.15%); unipolar aHR 1.20 (0.74–1.95)[9,10]
- **Case series:** 281 pooled, no gambling, no compulsive shopping[11]

**Why.** In PD, denervation alters receptor coupling and availability; not the case in depression.[13,14]

**Aripiprazole.** Shows a comparable rate and an FDA warning in the label but is not a factor clinically.[12]

*1 Weintraub et al, Arch Neurol 2010 · 2 Corvol et al, Neurology 2018 · 3 Rabinak & Nirenberg, Arch Neurol 2010 · 4 Browning et al, Lancet Psychiatry 2025 · 5 Corrigan et al, Depress Anxiety 2000 · 6 Cusin et al, J Clin Psychiatry 2013 · 7 Franco-Chaves et al, J Affect Disord 2013 · 8 Ventorp et al, Nat Med 2026 · 9 Lindström et al, J Affect Disord 2026 · 10 Lindström et al, Front Psychiatry 2026 · 11 Tundo et al, Life 2023 · 12 Etminan et al, J Clin Psychopharmacol 2017 · 13 Prieto et al, J Neurophysiol 2011 · 14 Mizuno et al, J Psychopharmacol 2023*

# Other Programs

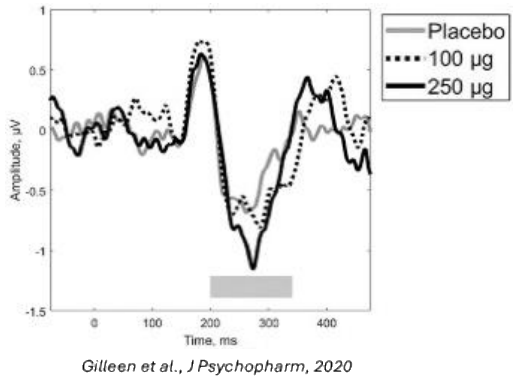
# ALTO-101

## Development for CIAS

# ALTO-101, a novel PDE4 inhibitor, in development for CIAS with a validated mechanism and demonstrated pro-cognitive activity

**1** *PDE4i represents a historically validated mechanism for cognition*

PDE4 inhibition has shown clear pro-cognitive effects in humans (including CIAS)

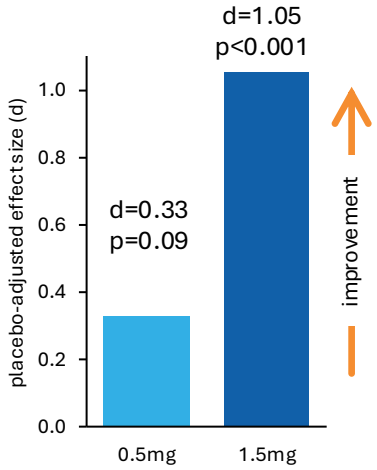



*Gilleen et al., J Psychopharm, 2020*

*Historical roflumilast studies provide external support for ALTO-101 in cognition and EEG*

**2** *Direct effects on best EEG biomarker of CIAS*

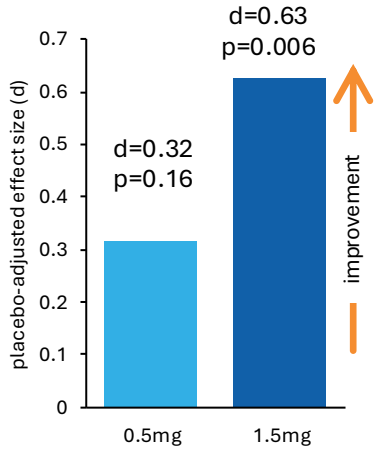
**Theta response (placebo-adjusted)**




*ALTO-101 demonstrated statistically significant effects vs. placebo on theta response in Ph. 1*

**3** *ALTO-101 demonstrated clear pro-cognitive effects in humans*

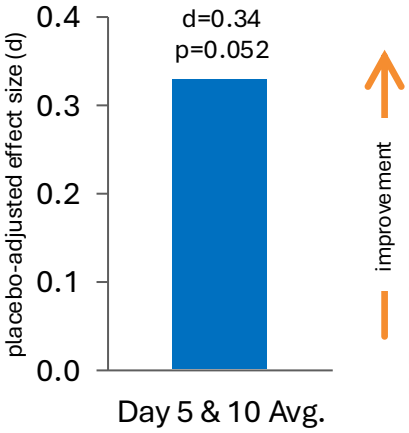
**Processing speed (placebo-adjusted)**




*Good correlation between theta response & cognition, supported by ALTO-101 effects on cognition in human Phase 1 study*

**4** *PoC study in CIAS showed compelling EEG signals with 10-day crossover design*

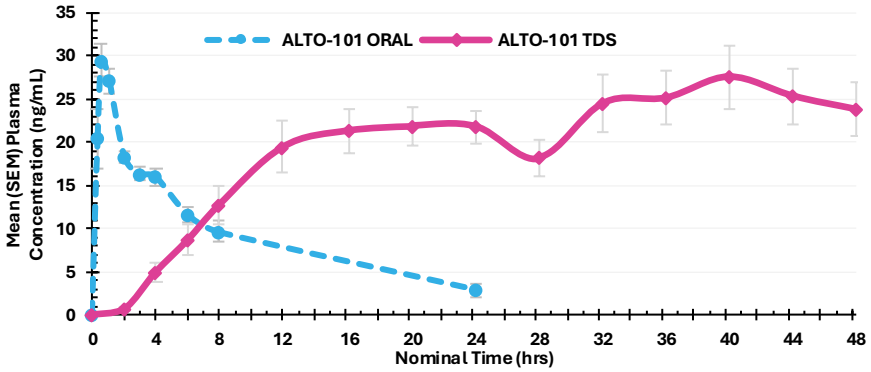
**Theta response (placebo-adjusted)**




*ALTO-101 demonstrated compelling EEG effects on Theta measures in PoC study*

# Formulation innovation for greater drug exposure and improved tolerability profile

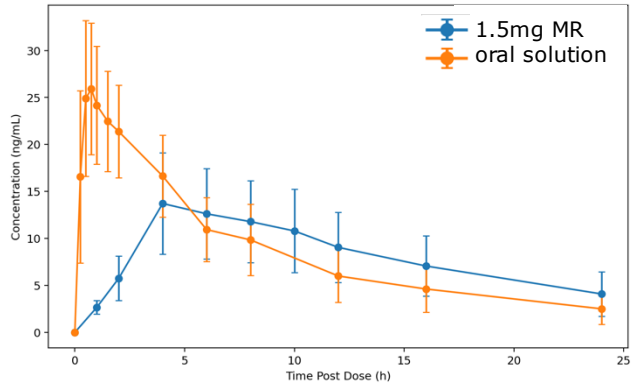
## Transdermal delivery system




| Related Adverse Events >5% | ALTO-101 Oral Solution (1mg) (N = 15) | ALTO-101 TDS Formulation (N = 14) |
|---|---|---|
| **PDE-4i Class-Related AEs** | | |
| Dizziness, n (%) | 6 (40.0) | 1 (7.1) |
| Nausea, n (%) | 3 (20.0) | 0 |
| Diarrhea, n (%) | 1 (6.7) | 0 |
| Dyspepsia, n (%) | 1 (6.7) | 0 |
| Vertigo, n (%) | 1 (6.7) | 0 |
| **Other AEs** | | |
| Headache, n (%) | 2 (13.3) | 5 (35.7) |
| Administration site pruritus, n (%) | 0 | 2 (14.3) |
| Asthenia, n (%) | 1 (6.7) | 0 |

TDS formulation, with delayed Tmax and lower Cmax, demonstrated significant reduction/elimination of PDE4i related AEs

## Oral modified-release




| Related Adverse Events >5% | ALTO-101 Oral Solution (1mg) (N = 20) | ALTO-101 MR 1.5mg (N = 19) | ALTO-101 MR 3mg (N = 17) |
|---|---|---|---|
| **PDE-4i Class-Related AEs** | | | |
| Nausea, n (%) | 5 (25) | 0 | 0 |
| Dizziness, n (%) | 1 (5) | 0 | 0 |
| Vomiting, n (%) | 1 (5) | 0 | 0 |
| **Other AEs** | | | |
| Headache, n (%) | 4 (20) | 0 | 0 |
| Fatigue, n (%) | 1 (5) | 0 | 0 |

Oral modified release:

- Clear tolerability benefits over immediate release – very low rates of PDE4i-related AEs → similar to TDS formulation
- Patents covering formulation and release profile

# PDE4 inhibition is relevant across numerous high-need therapeutic areas

Available medications are non-brain penetrant and only approved outside CNS – both come with substantial tolerability and dosing limitations

**$2.3bn**

**2025 SALES**

Otezla® (apremilast) 30mg tablets

**$0.3bn**

**2021 SALES**

Daliresp® (roflumilast) tablets

## NON - CNS INDICATIONS

- **Plaque Psoriasis**
- **Psoriatic Arthritis**
- **COPD**
- Asthma
- Atopic Dermatitis
- Psoriasis & Eczema
- Rosacea
- Palmoplantar Pustulosis
- Nummular Eczema
- Pruritus
- Rheumatoid Arthritis
- Lupus (SLE)
- Crohn's
- Idiopathic Pulmonary Fibrosis

***Bold denotes approved indications***

**ALTO-101**

ALTO NEUROSCIENCE

## CNS

- Schizophrenia
- Bipolar
- PTSD
- Depression
- Substance Dependence
- Multiple Sclerosis
- Fragile X
- Allergic Encephalomyelitis
- ALS
- Migraine
- Glioblastoma
- Alzheimer's
- Huntington Disease
- Anxiety Disorders
- Dementia
- Cerebrovascular Disorder
- Mild Cognitive Impairment
- ADHD
- Parkinson’s Disease
- Autism Spectrum Disorders
- Frontotemporal Dementia
- Developmental Delay
- Learning Disabilities

# ALTO-203

## Novel H3 inverse agonist

# ALTO-203: An investigational H3 inverse agonist with effects across multiple major neurotransmitter systems

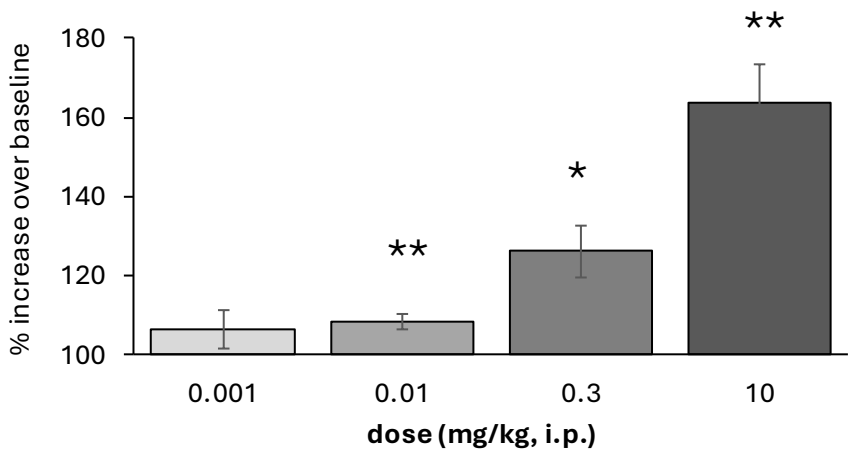



Region- and receptor-specific effects
(mood, cognition, energy, motivation, wakefulness)

| | Main effect of enhancing release |
|---|---|
| **Dopamine** | • Mood<br>• Reward Processing<br>• Sustained Attention |
| **Norepinephrine** | • Alertness<br>• Sustained Attention |
| **Acetylcholine** | • Sustained Attention<br>• Learning and Memory |
| **Histamine** | • Wakefulness |

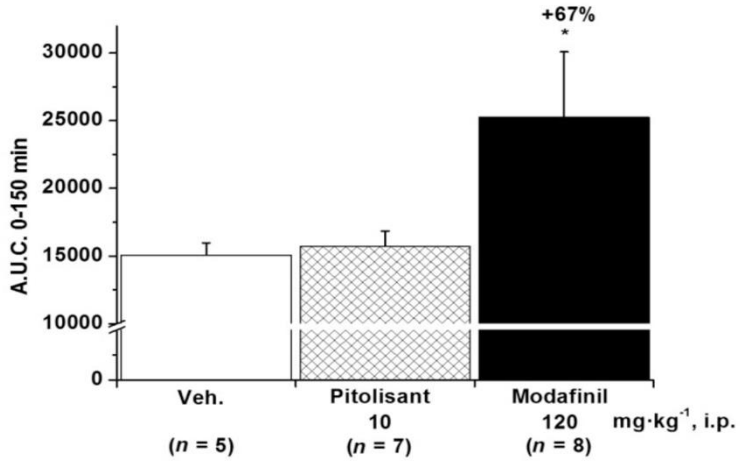
# ALTO-203 showed ability to increase reward system dopamine, unlike the only approved H3 (pitolisant)*

ALTO-203 increases dopamine release in the reward system (nucleus accumbens) in a dose-related manner




ALTO-203 results plotted as percent increase over baseline from 0-150min post-dose, to compare to timing of pitolisant/modafinil study outcome (* p<0.05; ** p<0.01)

Pitolisant does not increase reward system dopamine (modafinil used as a comparator)




*Uguen et al., BJP, 2013*

*Study conducted prior to Alto acquisition

# Positive pharmacodynamic effects from exploratory proof-of-concept study of ALTO-203

*Effects replicated key findings from completed Phase 1 study*

## Study Population:

Patients with MDD with anhedonia and who were not on an antidepressant (monotherapy)

## Design:

Two sequential double-blind, placebo-controlled treatment periods:

- **Single-dose:** randomized, 3-way crossover. Evaluation of PD measures (positive emotion, cognition, reward processing tests)
- **Multi-dose:** Participant continues to take Tx #3 dose once daily for 28 days. Focus on safety and PK but will also measure MDD and anhedonia symptoms

## Number of participants:

63 completers of 3-way crossover (single-dose period)

## Topline pre-specified results

***Identified an EEG biomarker predictive of patient response***

- *Theta/beta ratio: commonly used EEG index of cortical arousal and attentional control*

| | Phase 1 | Phase 2a |
|---|---|---|
| **Improvements in alertness, mood** | ☑ | ☐ *High placebo response* |
| **Improvements in sustained attention** | ☑ | ☑ |
| **Reduction in EEG theta/beta ratio** | ☑ | ☑ |
| **Increase in wakefulness** | ☑ | ☑ |
| **Greater attention improvements in high theta/beta individuals** | ☑ | ☑ |

ALTO NEUROSCIENCE