Testimony Before the FDA's Psychopharmacologic Drugs and Drug Safety and Risk Management Advisory Committees

Olanzapine/samidorphan (OLZ/SAM)

NDA 213,378 (ALK3831) for schizophrenia or bipolar

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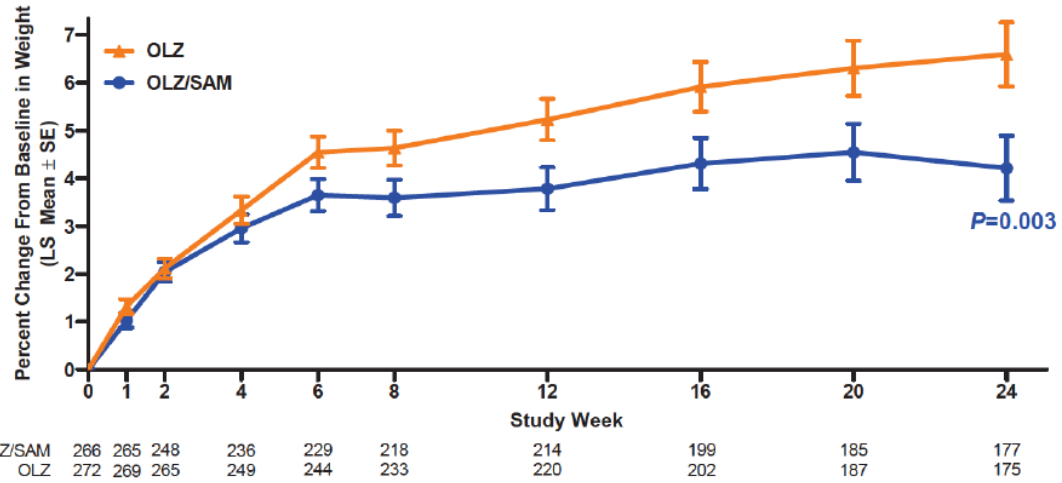
Michael T. Abrams, MPH, PhD
Public Citizen's Health Research Group

I have no financial conflicts of interests

Efficacy: Slide 36 Alkermes (Dr. McConnell), Slide 41 FDA (Dr. Southammakosane)

Less Mean Weight Gain with OLZ/SAM (A303)



OLZ/SAM	266	265	248	236	229	218	214	199	185	177
OLZ	272	269	265	249	244	233	220	202	187	175

LS = least squares; SE = standard error
Based on analysis of covariance (ANCOVA) approach using multiple imputation (MI) for missing data.
The numbers under the figure indicate the number of patients at each time point based on observed data.

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Clinical Summary: Weight Mitigation

FDA

Study A303

- Primary and secondary weight endpoints statistically significant
  - Percent change from baseline: ALKS 3831 4.21%, olanzapine 6.59%
    - Mean weight difference: -2.4% (95% CI: -3.9, -0.9)
  - Proportion with ≥10% weight gain: ALKS 18% vs. OLZ 30%
  - Proportion with ≥7% weight gain: ALKS 28% vs. OLZ 43%
- Missing data and lack of long-term control arm
- Favorable waist circumference and blood pressure changes
- Mixed metabolic laboratory results- unfavorable glycemic trends

Study 302

- Olanzapine-subtracted weight change not dose-related: -1.2% to -1.9%
- No notable changes in waist circumference, metabolic laboratory results, and blood pressure

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- Absolute difference in weight gain of about 2% at 24 weeks
- Mixed and mostly null effects on metabolic indicators

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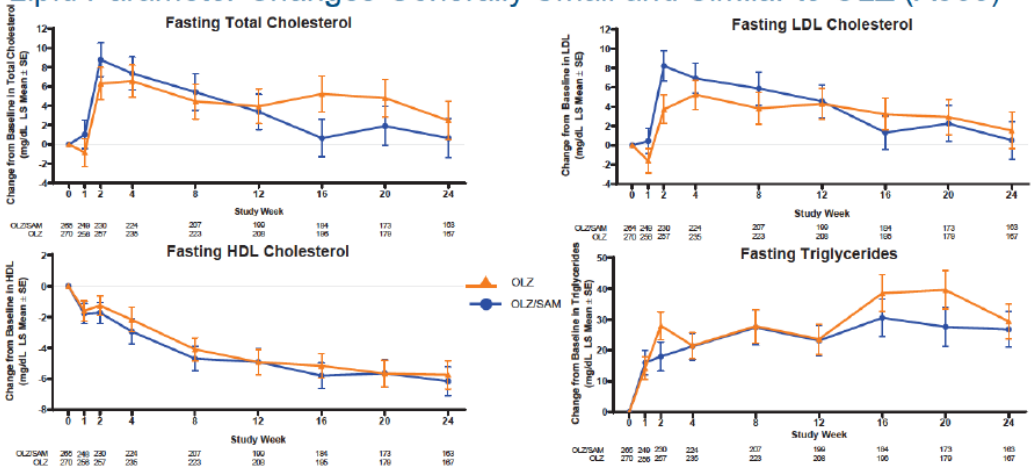
Efficacy: Slide 45 & 46 Alkermes (Dr. McDonnell)

Lipid Parameter Changes Generally Small and Similar to OLZ (A303)



- Lipid parameters stable over long term (A303+EXT [Stable])

HDL = high-density lipoprotein; LDL = low-density lipoprotein; LS = least squares; SE = standard error
Based on mixed model with repeated measurements (MMRM) using observed data.

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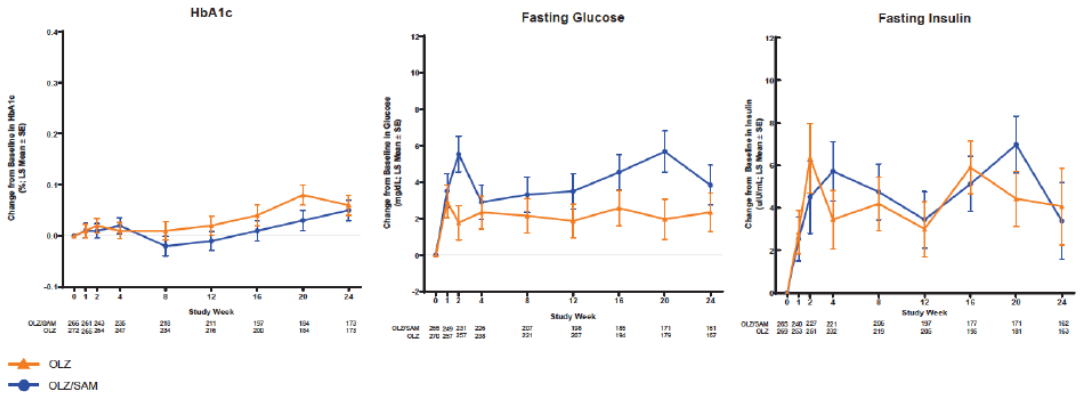
Glycemic Parameter Changes Generally Small and Similar to OLZ (A303)



- Glycemic parameters stable over long term (A303+EXT [Stable])

HbA1c = hemoglobin A1c; LS = least squares; SE = standard error
Based on mixed model with repeated measurements (MMRM) using observed data.

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➢ Null effects on other metabolic indicators

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Safety: Slide 71 Alkermes (Dr. Yagoda); Slide 52 FDA (Dr. Mallama, Slide 10)

Prevalence of Opioid Use Disorder (OUD) – Schizophrenia, Bipolar Disorder

- US general population = ~0.7 – 2.1%[a,b]
- Schizophrenia population = ~5.1%[c]
- Bipolar disorder population = ~4.3 – 8.5%[d,e]

[a] SAMHSA. HHS Publication No. PEP 19-5068, NSDUH Series H-54; 2019.
[b] Saha et al., J Clin Psych 2016.
[c] Hunt et al., Drug Alcohol Depend. 2018.
[d] Cerullo et al., Subst Abuse Treat Prev Policy. 2007.
[e] Hunt et al., J Affect Disorders. 2016.

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Drug Utilization Data Related to Risk Scenario #2: Inadequately Controlled Pain

FDA

National estimates of patients* who received a dispensed prescription for olanzapine and opioid containing products concurrently or as individual agents, by patient age, from U.S. outpatient retail pharmacies, 2019**

	2019		
	Total olanzapine patients (N)	Patients receiving concurrent opioids	
		Patients (N)	Share (%)
Olanzapine	**1,606,521**	**338,978**	**21.1%**
<18 years	92,898	3,689	4.0%
18-64 years	1,230,949	258,442	21.0%
65+ years	282,303	76,821	27.2%
Unknown age	49	17	34.1%

Source: Symphony Health database. 2019. Extracted August 2020.; *The patient counts are pulled and projected at each unique level of reporting. For this reason, the age breakouts may not sum to unique projected total patients. **Opioid containing products consist of claims for products that contain any opioids which include opioid analgesics, cough/cold products, tramadol, and combination products

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- Major safety, adverse effects concerns: risk of overdose, and risk of inadequate pain control when needed

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Overall indicator: Slide 25 FDA (Dr. Southammakosane)

Study A303: Quality of Life

	ALKS 3831	Olanzapine
N	266	272
IWQOL Total Score Baseline Mean (SD)	89.6 (15.12)	88.0 (15.31)
Change from Baseline n	177	172
LS Mean (SE)	0.9 (0.89)	0.8 (0.89)
EQ-5D-5L Index Score Baseline Mean (SD)	0.84 (0.160)	0.83 (0.154)
Change from Baseline n	176	172
LS Mean (SE)	0.02 (0.010)	0.01 (0.010)

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[Source: FDA generated]

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- No apparent improvement in this patient-reported outcome

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Conclusions/Recommendations

- Benefits appear marginal at best, 2%, for weight only (not other metabolic indicators); No improvement in QoL.
- Opioid antagonist use risks are substantial, especially for this population given high rates of substance use disorders, medication discontinuity, and the need for analgesia
- **Recommendation to the advisory committees**: Vote "No" on the following questions:
  - Has the Applicant presented adequate evidence that samidorphan meaningfully mitigates olanzapine-associated weight gain?
  - Has the Applicant adequately characterized the safety profile of ALKS3831?
  - Is labeling sufficient to mitigate the risks related to the opioid antagonist action of samidorphan?
- **Recommendation to the FDA:** Do not approve olanzapine/samidorphan

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