Human Metabolism

Process	Enzyme System	K_i
• Primary		
– Glucuronidation (10-N, 4'-N)	--	--
– 4'-N-demethylation	CYP-P450-1A2	36µM
(Olanzapine metabolism decreased in non-smokers, females, geriatric population)		
– 2-methyl-hydroxylation	CYP-P450-2D6[a]	89µM
(Olanzapine metabolism not different in 2D6 deficient subjects)		
– 4'-N-oxidation	FMO system	--

Note: No significant in vitro affinity for CYP-P450-2C9[a], CYP-P450-2C19[a], CYP-P450-3A[a]

[a]In vivo drug interaction studies demonstrate no influence of olanzapine on drugs metabolized through these systems

Human Metabolism (continued)

- Secondary
  - Oxidation of 2-hydroxymethyl metabolite
  - Further glucuronidation

Human Metabolites

- *10-N-glucuronide[a,b]: Major plasma and urinary metabolite*
- *Olanzapine[a,b]: 28% of plasma radioactivity at T_{max}*
- *4'-N-desmethylolanzapine[a,b]: in plasma, 44% of parent*
- *2-hydroxymethylolanzapine[a]*
- *Olanzapine-4'-N-oxide[a,b]*
- *4'-N-glucuronide[b]: Major urinary metabolite*
- *2-carboxyolanzapine[b]*
- *2-carboxyglucuronide[b]*
- *2-carboxyolanzapine-4'-N-oxide[b]*
- *2-carboxy-4'-N-desmethylolanzapine[b]*

Note: 4'-N-desmethylolanzapine and 2-hydroxymethylolanzapine have some affinity for D_2, D_1, 5-HT_{2A} receptors; no metabolite studied to date active in vivo

[a]*Detectable in plasma*

[b]*Detectable in urine; account for 60% urinary radiocarbon recovery (54% total radiocarbon), 3 additional urinary peaks*

OLANZAPINE CLINICAL DEVELOPMENT:

Molecule To Drug Candidate

OLANZAPINE

Lilly

Development Milestones

Synthesis:	4/29/82
IND filed:	7/24/86
First human dose:	9/10/86
First open-label clinical dose:	12/9/88
First double-blind, placebo-controlled efficacy dose:	11/21/91
Completion of core studies:	2/14/95
World wide regulatory submission filed:	9/21/95

Human Exposure (2/14/95)

≥ 1 Dose:	3,139
> 1 Month:	>1,962
> 6 Months:	>876
> 1 Year:	>301

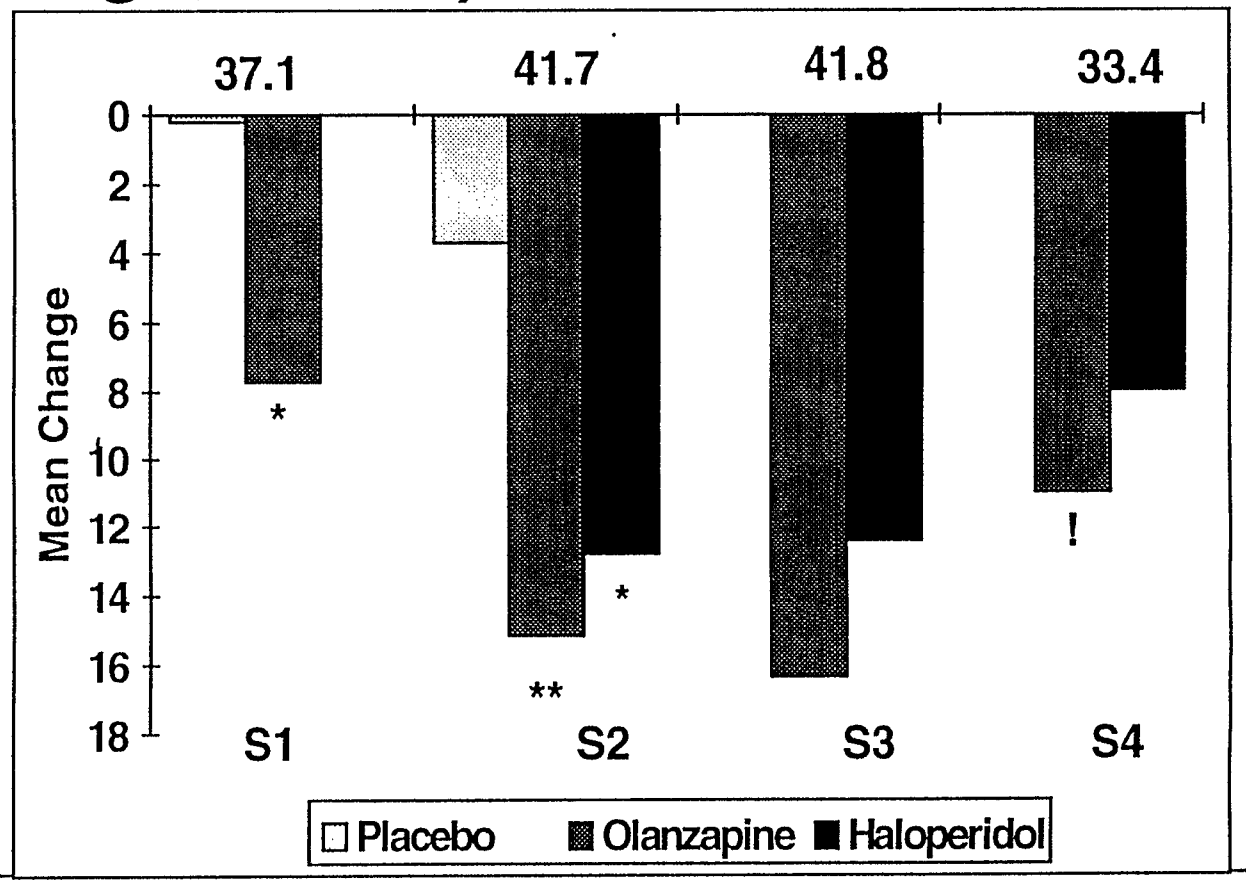
Core Studies (All Double-Blind)

- Study 1 (S1)
  - N=152
  - Schizophrenia, inpatient, $BPRS_{0-6} \geq 24$
  - 6 weeks
  - Placebo, olanzapine 1 mg/day, olanzapine 10 mg/day
- Study 2 (S2)
  - N=335
  - Schizophrenia, inpatient, $BPRS_{0-6} \geq 24$
  - 6 weeks, extension
  - Placebo, olanzapine 2.5 - 7.5 mg/day, olanzapine 7.5 - 12.5 mg/day, olanzapine 12.5 - 17.5 mg/day, haloperidol 10 - 20 mg/day

Core Studies (All Double-Blind)

- Study 3 (S3)
  - N=431
  - Schizophrenia, inpatient, BPRS $_{0\text{-}6} \geq 24$
  - 6 weeks, extension
  - Olanzapine 1 mg/day, olanzapine 2.5 - 7.5 mg/day, olanzapine 7.5 - 12.5 mg/day, olanzapine 12.5 - 17.5 mg day, haloperidol 10 - 20 mg/day
- Study 4 (S4)
  - N=1,996 (randomization - 2 olanzapine:1 haloperidol)
  - Schizophrenia/schizophreniform disorder/schizoaffective disorder, in-/outpatient, BPRS $_{0\text{-}6} \geq$ 18, or intolerant of current therapy
  - 6 weeks, extension
  - Olanzapine 5 - 20 mg/day, haloperidol 5 - 20 mg/day

Efficacy: BPRS - Total Score (Mean change, LOCF)



*p ≤ .050 vs placebo
**p ≤ .001 vs placebo
!p ≤ .050 vs haloperidol

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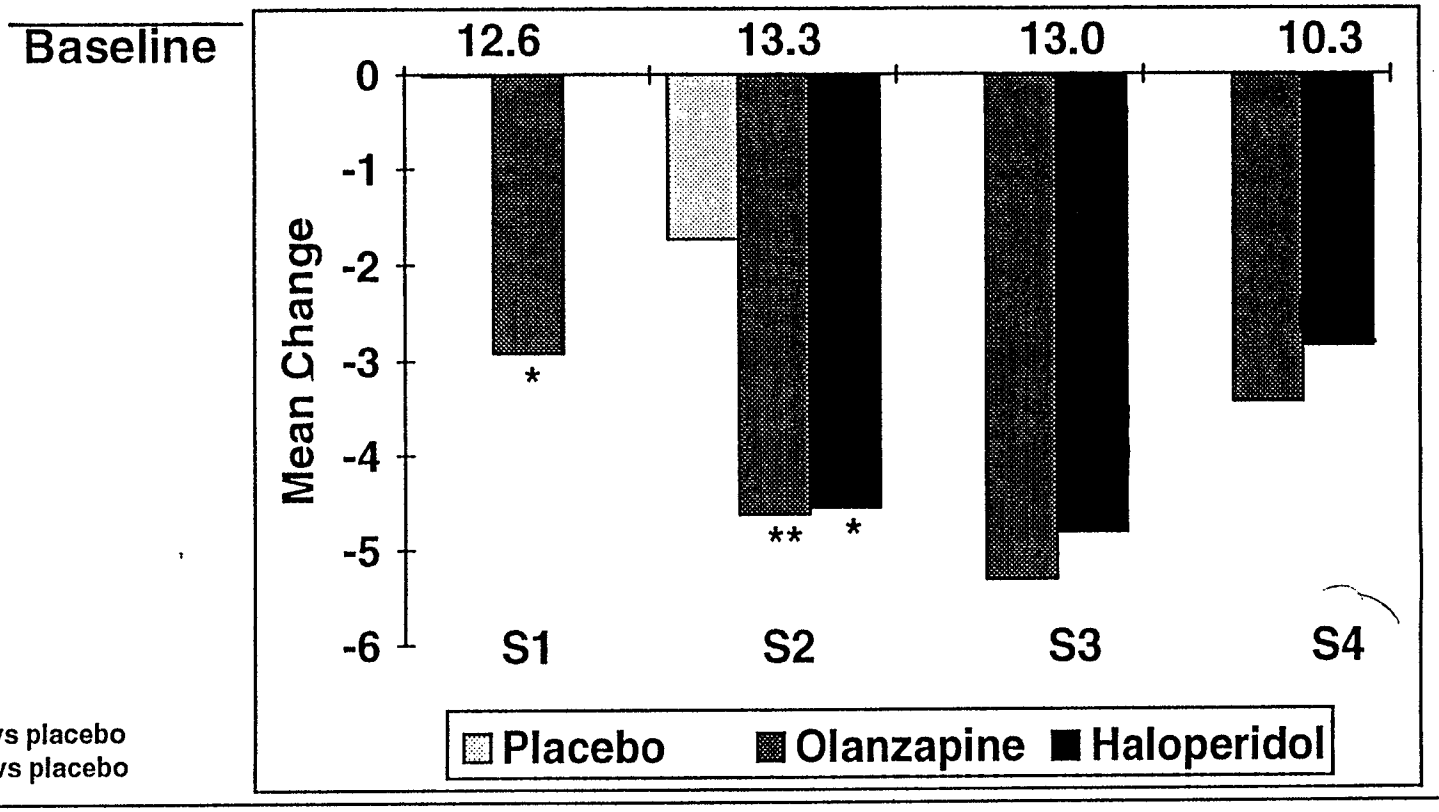
Efficacy: BPRS - Positive Score (Mean change, LOCF)



*p ≤ .050 vs placebo
**p ≤ .010 vs placebo

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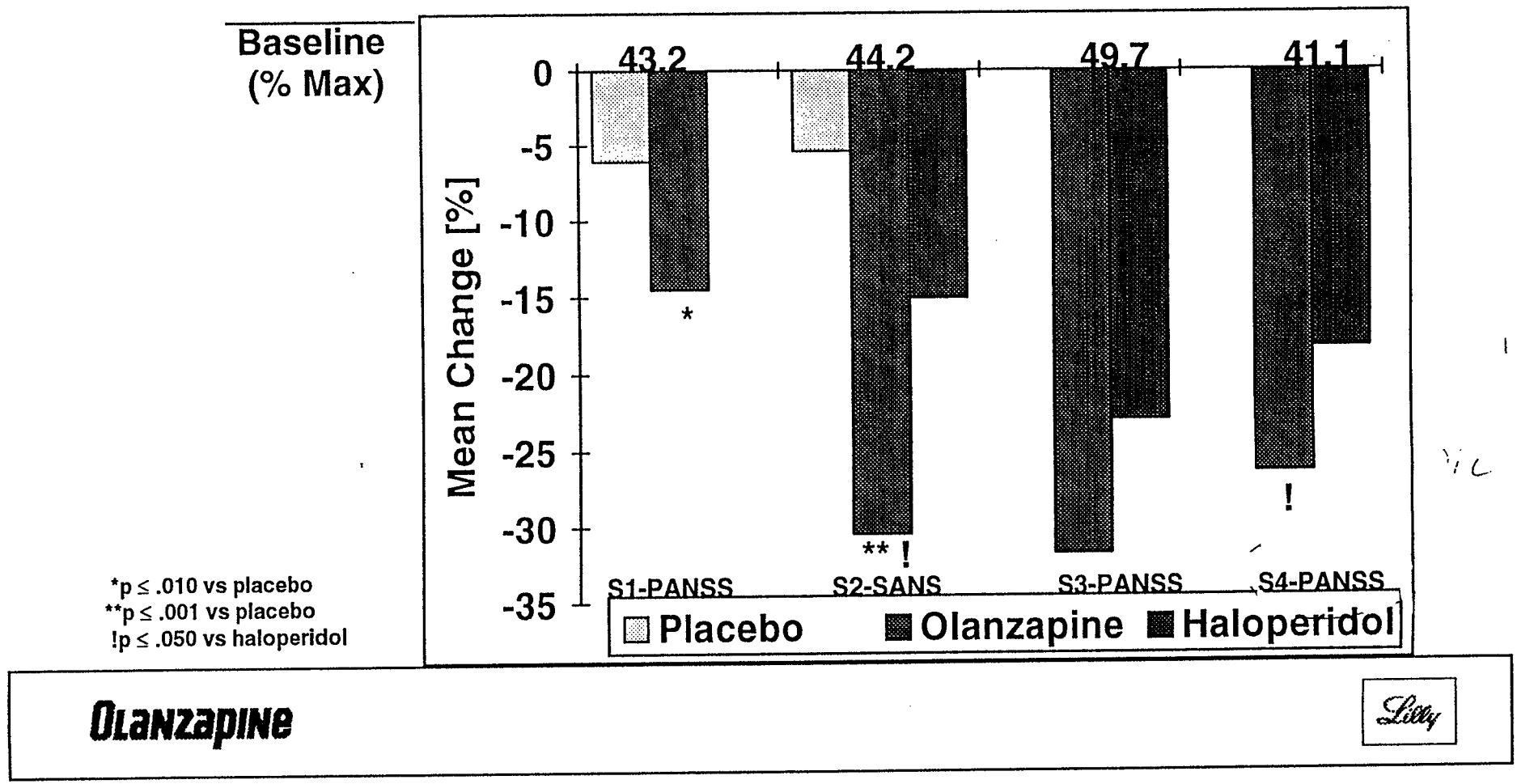
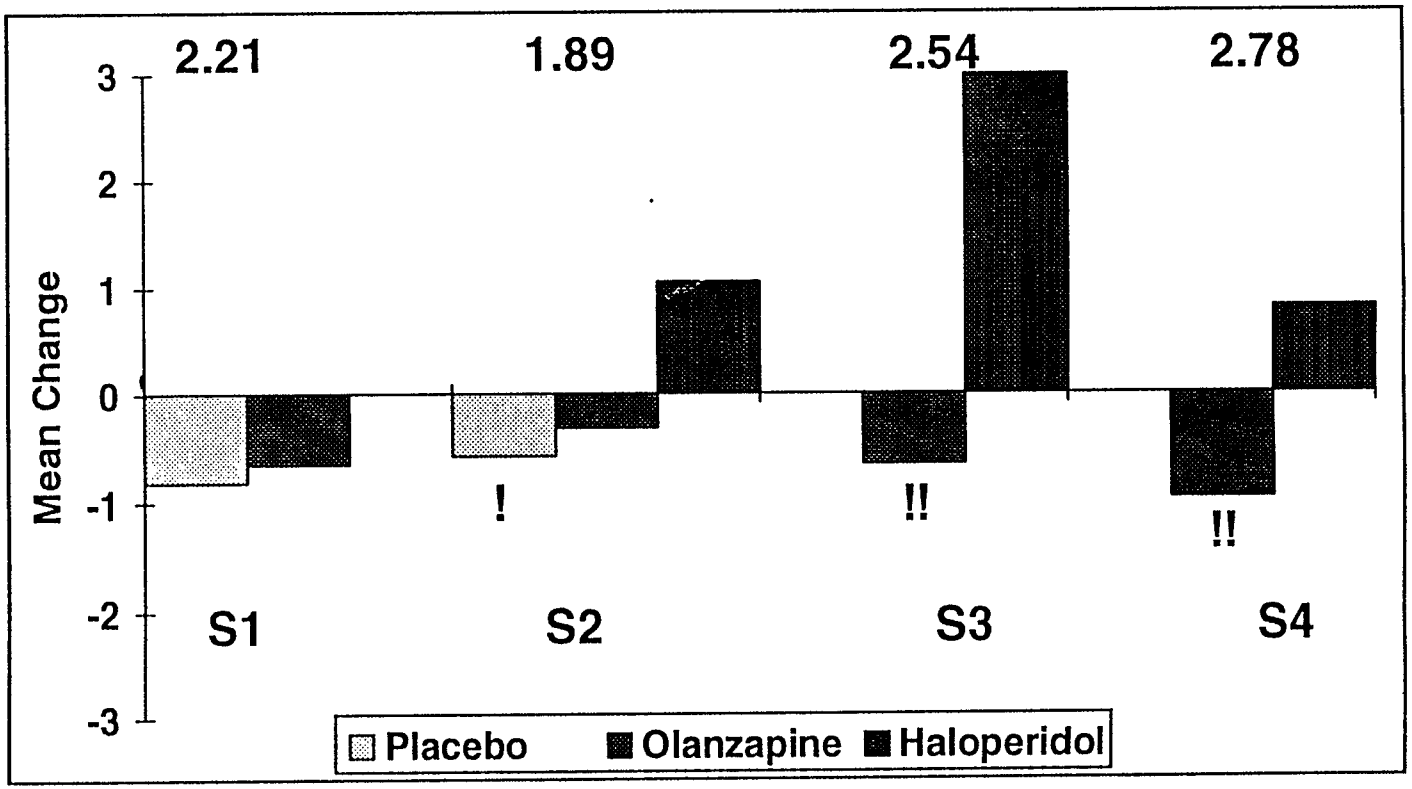
Efficacy: Negative Symptom Scales (Mean change [%], LOCF)



Acute EPS: Simpson-Angus Scale (Mean change, LOCF)

Baseline



!p ≤ .050 vs haloperidol
!!p ≤ .001 vs haloperidol

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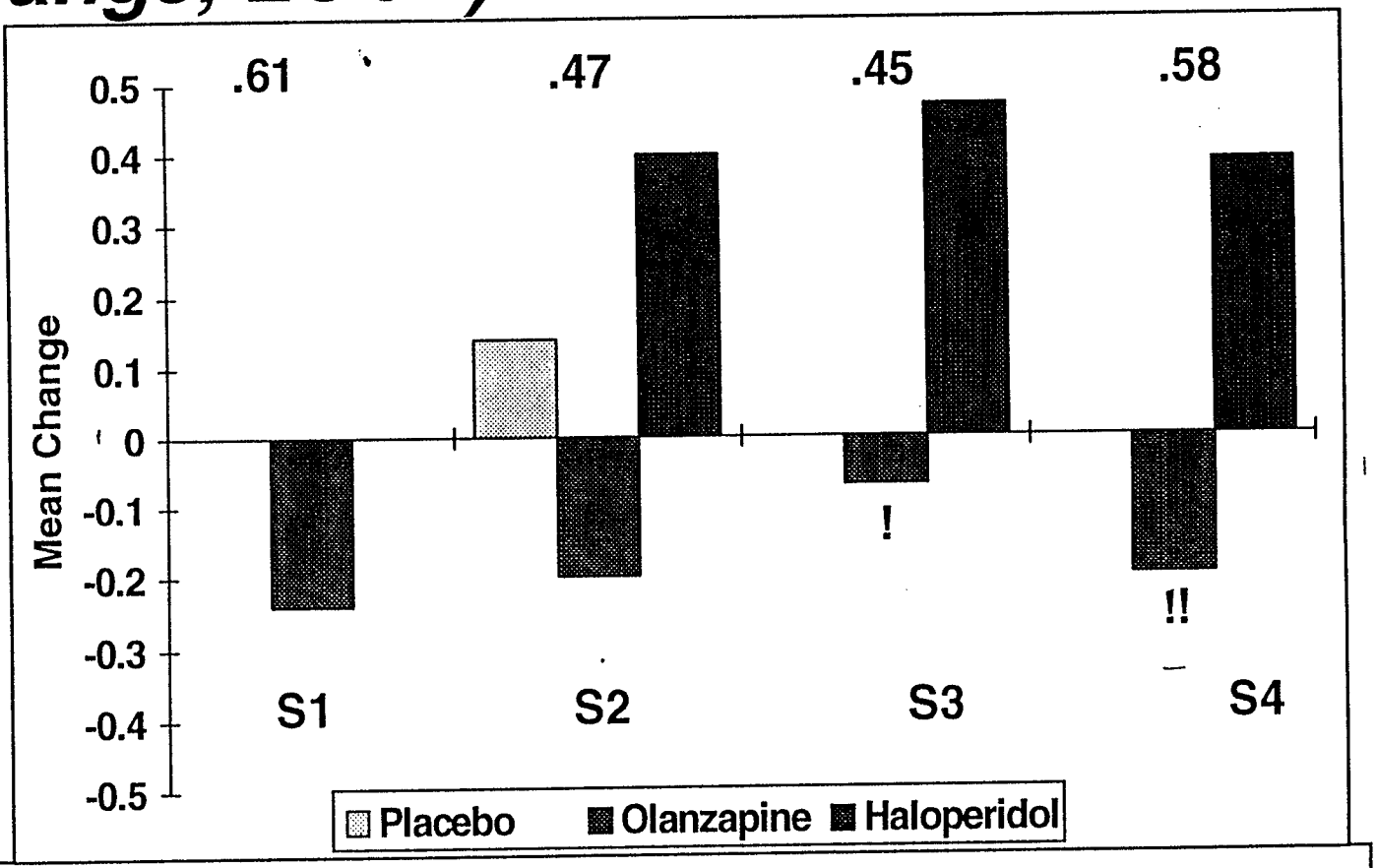
Acute EPS: Barnes Akathisia Scale (Mean change, LOCF)

Baseline



!p ≤ .010 vs haloperidol
!!p ≤ .001 vs haloperidol

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Long-Term Treatment Emergent Dyskinesia

- Methods
  - Double-blind extensions of HGAD, E003, HGAJ
    - Median exposure: OLZ - 237 days, HAL - 203 days (range 6 wk - 3+ yr.)
  - Definition: Cross-sectional RDC criteria for TD assessed by items 1-7 of AIMS
    - 1+ item $\geq$ 3, or 2+ items $\geq$ 2
  - No historical or secondary condition of TD and failure to meet cross-sectional RDC criteria at baseline

Long-Term Treatment Emergent Dyskinesia (continued)

- Results

Longitudinal persistance	Olanzapine (N=707)	Haloperidol (N=197)	p-Value
Any postbaseline assessment	50 (7.1%)	32 (16.2%)	<.001
Final AIMS assessment	16 (2.3%)	15 (7.6%)	<.001
Final 2 AIMS assessment	7 (1.0%)	9 (4.6%)	.003

Adverse Events vs Placebo ($p \leq .05$ & $\geq 2\%$)

S1

	Olanzapine	Placebo
Anorexia	0%	10%
Delusions	0%	8%

Adverse Events vs Placebo ($p \leq .05$ & $\geq 2\%$)

	S2	
	Olanzapine	Placebo
Somnolence	39.1%	16.2%
Dizziness	17.4%	2.9%
Constipation	14.5%	0.0%
Pharyngitis	10.1%	1.5%
Paresthesia	0.0%	5.9%

Adverse Events vs Haloperidol

($p \leq .05$ & $\geq 2\%$)

	S4	
	Olanzapine	Haloperidol
Dry mouth	7.5%	4.2%
Weight gain	4.6%	1.8%
Increased appetite	4.0%	0.9%
Akathisia	6.5%	22.0%
Insomnia	10.4%	13.5%
Tremor	3.6%	12.6%
Hypertonia	3.2%	9.2%
Nervousness	5.7%	9.1%

Adverse Events vs Haloperidol ($p \leq .05$ & $\geq 2\%$) cont.

	S4	
	Olanzapine	Haloperidol
Extrapyramidal syndrome	2.1%	7.6%
Increased salivation	2.2%	6.4%
Vomiting	3.0%	5.9%
Joint disorder	1.9%	4.5%
Amblyopia	2.3%	4.4%
Anorexia	1.6%	3.3%
Dystonia	0.4%	2.9%
Weight loss	0.5%	2.0%

Vital Signs, Weight, ECG

- No change in resting vital signs
- Slight increase in orthostatic heart rate increase
- No change in orthostatic blood pressure decrease
- Weight gain dose related
- ECG: no change or slight increase in sinus rate with a corresponding decrease in QT interval

Laboratory Analytes

- *Transient, possibly dose-related increase in hepatic transaminases*
  - *No clinical symptoms*
  - *No discontinuations during acute phase of S4*
- *No evidence of hematotoxicity*
- *Mild, transient dose-related increase in prolactin*

Conclusions:

Efficacy

- Excellent overall and positive symptom efficacy
- Superior negative symptom efficacy

Conclusions:

Safety

- Mild sedation
- Mild anticholinergic effects
- Minimal subjective dizziness without orthostasis
- Some transient, asymptomatic hepatic transaminase elevations
- Minimal parkinsonism and akathisia with rare dystonias

Conclusions:

Atypical Profile

- Greater efficacy against negative symptoms than haloperidol
- Rare dystonic reactions and less parkinsonism and akathisia than with haloperidol
- Substantially less prolactin elevation than with haloperidol