ZYPADHERA

Olanzapine powder & solvent for prolonged release suspension for injection

Version 5.1: June 2013

Patients Treated with Depot Antipsychotics May…..

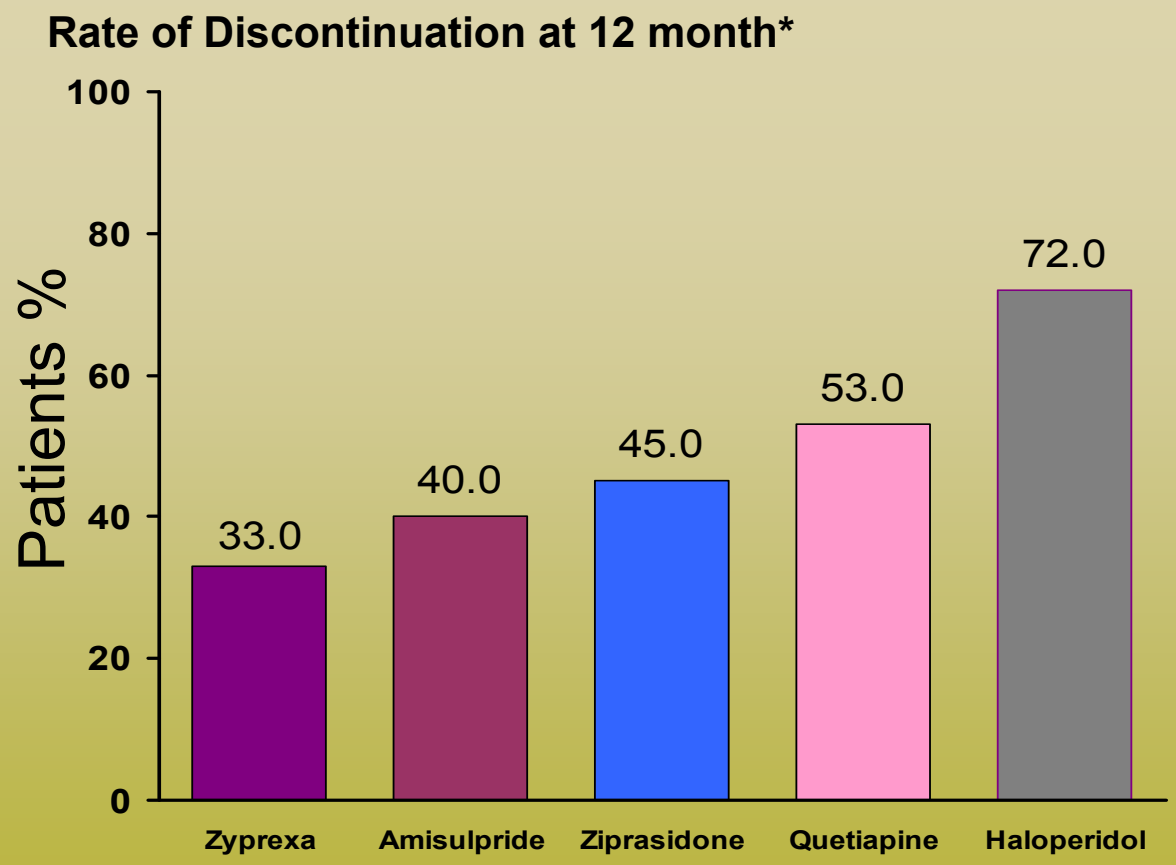
- Have had multiple **relapses** and/or recent hospitalizations
- Have a history of multiple **oral failures**
- Be struggling with **noncompliance**
- Be **symptomatic** – positive and/or negative symptoms
- Have a **lack of insight**

Additional Factors

Changes in Treatment Team	Lack of Adequate Efficacy
Co-morbid Substance Abuse	Issues with Medication Tolerability
Complexity of Medication Regimen	Inadequate Support System

Version 5.1: June 2013

Time to treatment discontinuation for any cause EUFEST Study (in first episode patients)



Treatment discontinuation for any cause differed between treatment groups (p<0.0001)

*Calculated from the Kaplan-Meier estimation

Kahn et al.Lancet 2008;371: 1085-1097

Achieving remission during 36 month SOHO Study follow-up compared with Zyprexa cohort

Quetiapine
OR 95%CI => 0.66 (0.56, 0.76)

Risperidone
OR 95%CI => 0.74 (0.66, 0.83)

Oral Typicals
OR 95%CI => 0.63 (0.55, 0.74)

Depot Typicals
OR 95%CI => 0.59 (0.50, 0.69)

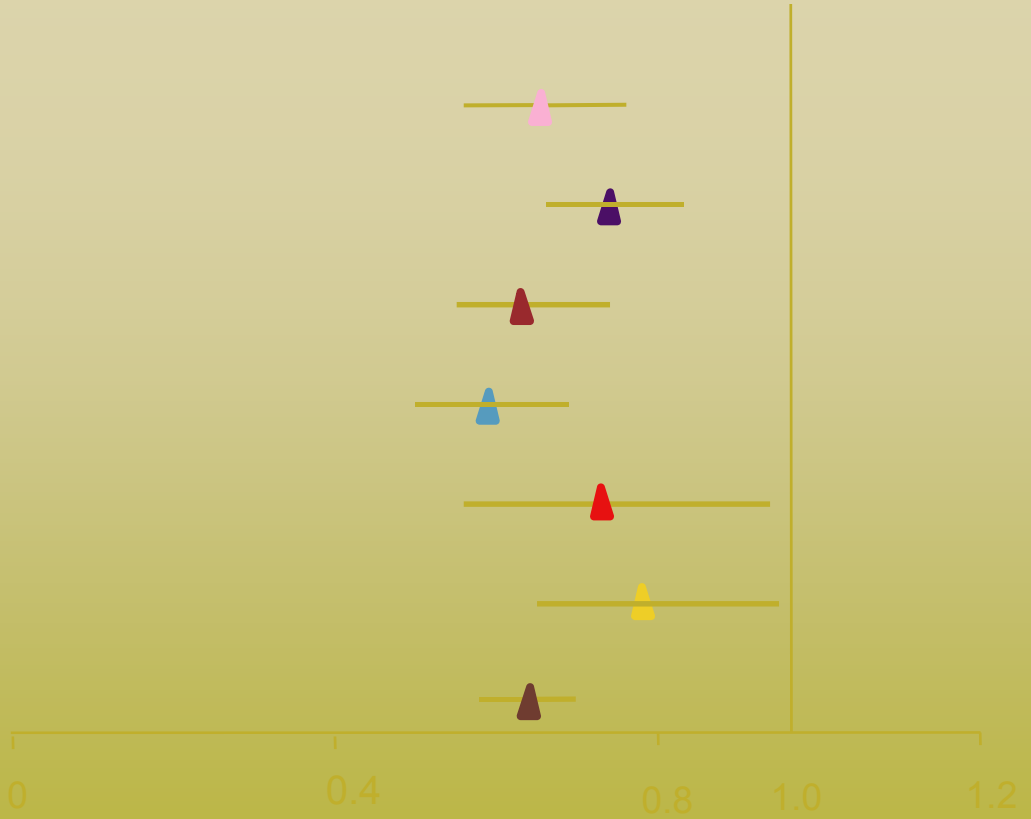
Amisulpride
OR 95%CI => 0.73 (0.56, 0.94)

Clozapine
OR 95%CI => 0.78 (0.65, 0.95)

2+Antipsychotics
OR 95%CI => 0.64 (0.58, 0.70)

Odds ratio and its 95% confidence interval

An odds ratio of <1 indicates a decreased likelihood of achieving remission



Adapted from Haro JM, et al. J Clin Psychopharmacol 2006;26:571-8.

Treatment Option

ZYPADHERA is indicated for the maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

- Olanzapine in a long-acting injectable form
- 2- and 4-week dosing options
- Does not require oral supplementation
- Efficacy over 8 week seen in acute study of symptomatic patients
- Efficacy similar to oral olanzapine seen over 24 weeks
- Safety similar to oral olanzapine except for Post Injection Syndrome

For full prescribing information and complete safety profile, please see the ZYPADHERA Summary of Product Characteristics

Version 5.1: June 2013

Training Content

At the end of this training, you should be able to:

- ✓ Describe what ZYPADHERA is and how it works
- ✓ Describe the efficacy of ZYPADHERA in symptomatic & in stable patients with schizophrenia
- ✓ Identify a post injection syndrome event in your clinical practice
- ✓ Know how to manage the risk of post injection syndrome
- ✓ Know what to do in case a post injection syndrome event occurs
- ✓ Differentiate between ZYPADHERA and Zyprexa IM to avoid medication errors
- ✓ Know how to monitor patients for metabolic changes
- ✓ Understand the dosing options with ZYPADHERA

ZYPADHERA

- **Deep intramuscular gluteal injection of olanzapine**
  - Not for deltoid injection
- **Administered once every 2 or 4 weeks**
  - Practically insoluble in water
  - Slowly dissolves at the injection site
- **3 vial strengths available (210mg, 300mg, 405mg)**
  - Reconstituted to a fixed concentration of 150 mg/ml

ZYPADHERA and Zyprexa IM –

Although both have olanzapine as their active ingredient and both are injected intramuscularly, they are intended for different indications

Category	ZYPADHERA	Zyprexa IM
Indication	**maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine**	**agitation associated with schizophrenia/ bipolar mania**
Generic Name	olanzapine powder & solvent for prolonged release suspension for injection	olanzapine for injection
Formulation	olanzapine pamoate suspension	olanzapine solution
Injection technique	IM, gluteal only	IM
Doses	150 mg/2wk, 210 mg/2wk, 405 mg/ 4wk, 300 mg/2wk	2.5 mg, 5 mg, 7.5 mg, 10 mg
Vial cap color & package lettering	terra cotta (210mg), celadon (300mg), or blue (405mg)	purple
Reconstitution	with special solvent provided in carton	with sterile water for injection
Appearance of medication in syringe	opaque yellow	clear yellow

Physicians should adhere to good prescribing practices.

Approximate Dose Correspondence Between ZYPADHERA and Oral Olanzapine*

Dose of Oral Olanzapine	ZYPADHERA every 2 weeks*	ZYPADHERA every 4 weeks*
10 mg/day	150 mg	300 mg
15 mg/day	210 mg	405 mg
20 mg/day	300 mg	–

***after 2 months of treatment**

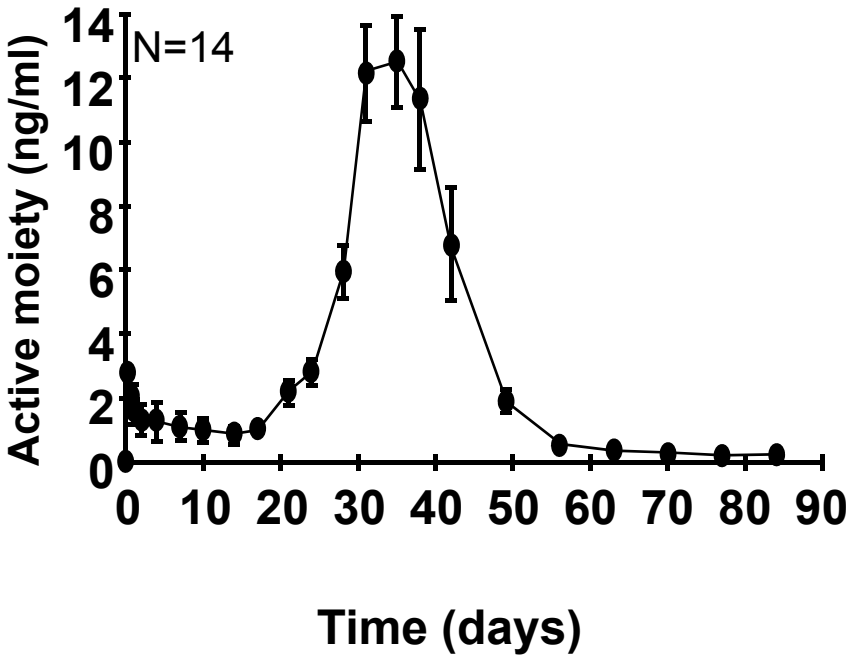
For full dosing information, please see the ZYPADHERA Summary of Product Characteristics

ZYPADHERA SPC:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000890/WC500054429.pdf

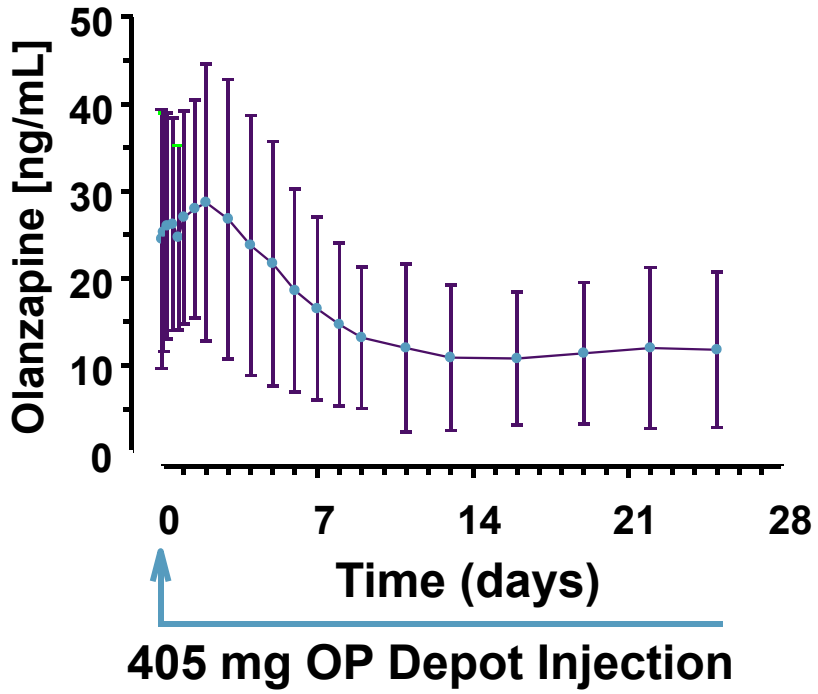
Version 5.1: June 2013

Mean Plasma Concentrations for a Single Risperdal Consta or ZYPADHERA Injection

Risperdal Consta 25 mg [1,2]

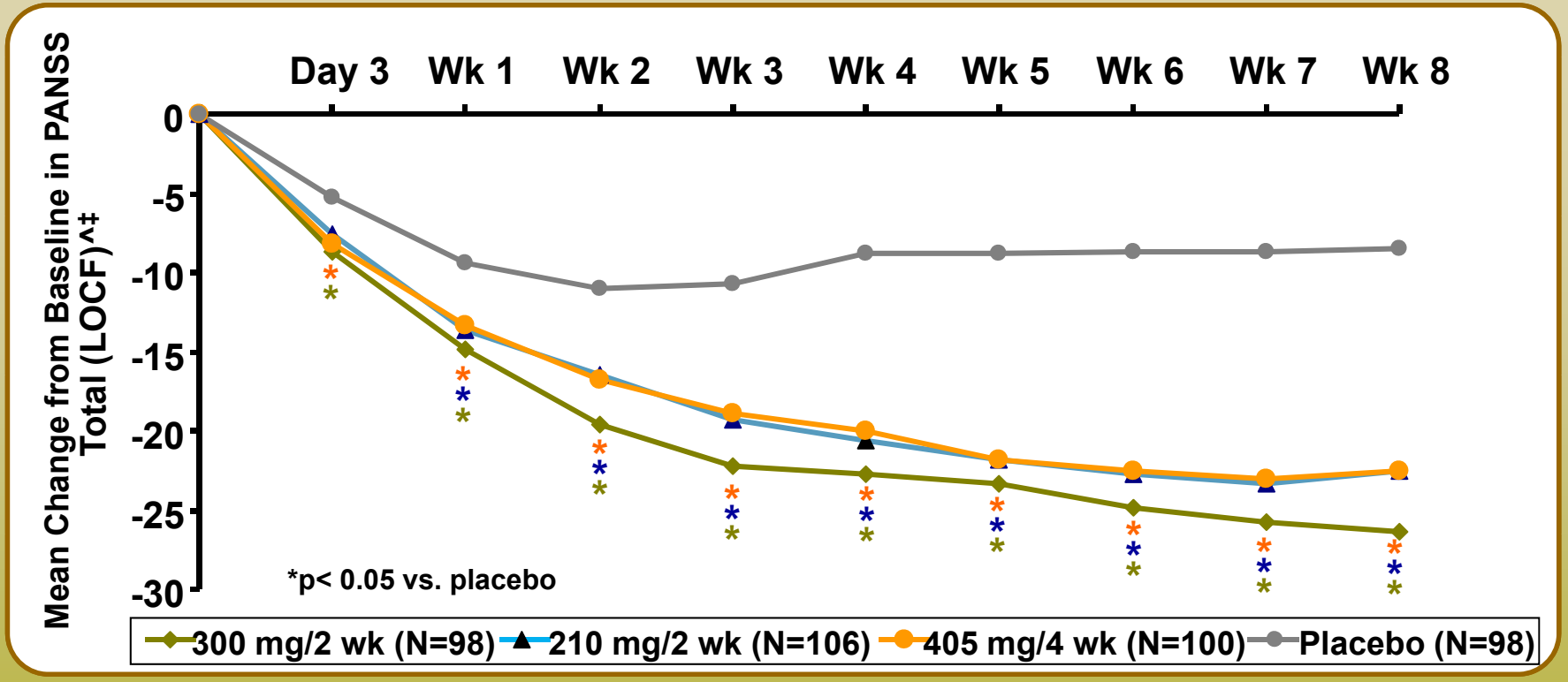


ZYPADHERA 405 mg [3]



1 Gefvert et al. *Int. J. of Neuropsychopharmacology*. 2005;8:27-36
2 Eerdekens et al. *Schizophrenia Research*. 2004;70:91-100
3 FDA website, accessed 8 May 2013: http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4338s1-00-index.htm

Mean Changes in PANSS Total Score of Patients with Schizophrenia Treated with ZYPADHERA or Placebo



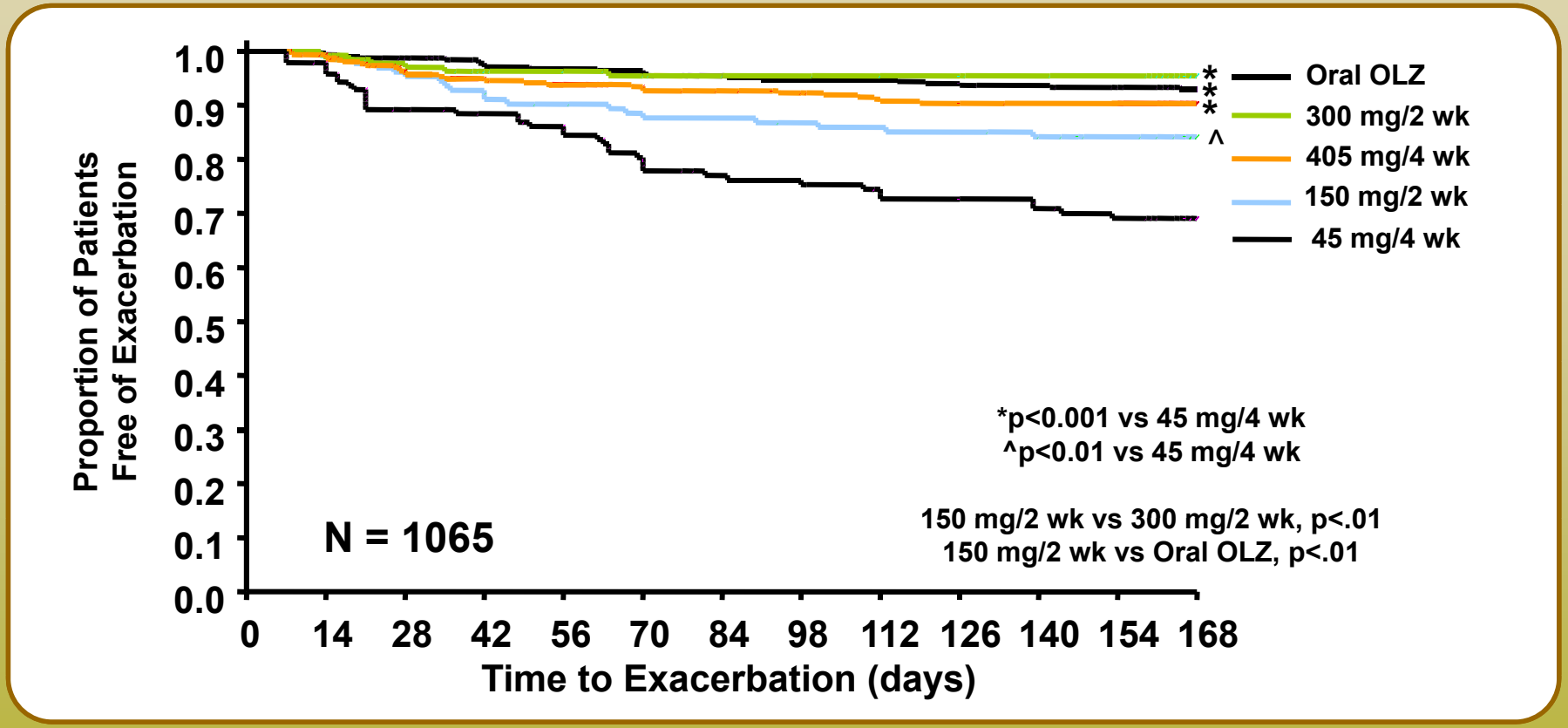
No oral antipsychotic supplementation was allowed at any time during the study

^primary endpoint: mean baseline to endpoint decrease (8 weeks) on PANSS
secondary efficacy measures at day 3 significant for two dosages
secondary efficacy measures at day 7 significant for the 3 dosages

‡LOCF = Last Observation Carried Forward

Lauriello, et al. *J Clin Psychiatry.* 2008;69:790-99.

Time to Exacerbation‡ with ZYPADHERA and Oral Olanzapine over 24 Weeks



No oral antipsychotic supplementation was allowed at any time during the study

‡ Exacerbation was defined a priori as an increase in positive symptoms or hospitalization for positive symptoms

Kane, Detke, Naber, et al. *Am J Psychiatry*. 2010;167:181-189.

Summary: Benefits of Treatment with ZYPADHERA

- Efficacy over 8 weeks seen in acute study of symptomatic patients
- Efficacy similar to oral olanzapine as seen over 24 weeks of maintenance treatment
- Oral antipsychotic supplementation not required
- 2- and 4-week dosing options

Comparable Safety Profile between ZYPADHERA and Oral Olanzapine: 24 Week Study

Treatment Emergent Adverse Events >2% in ZYPADHERA patients

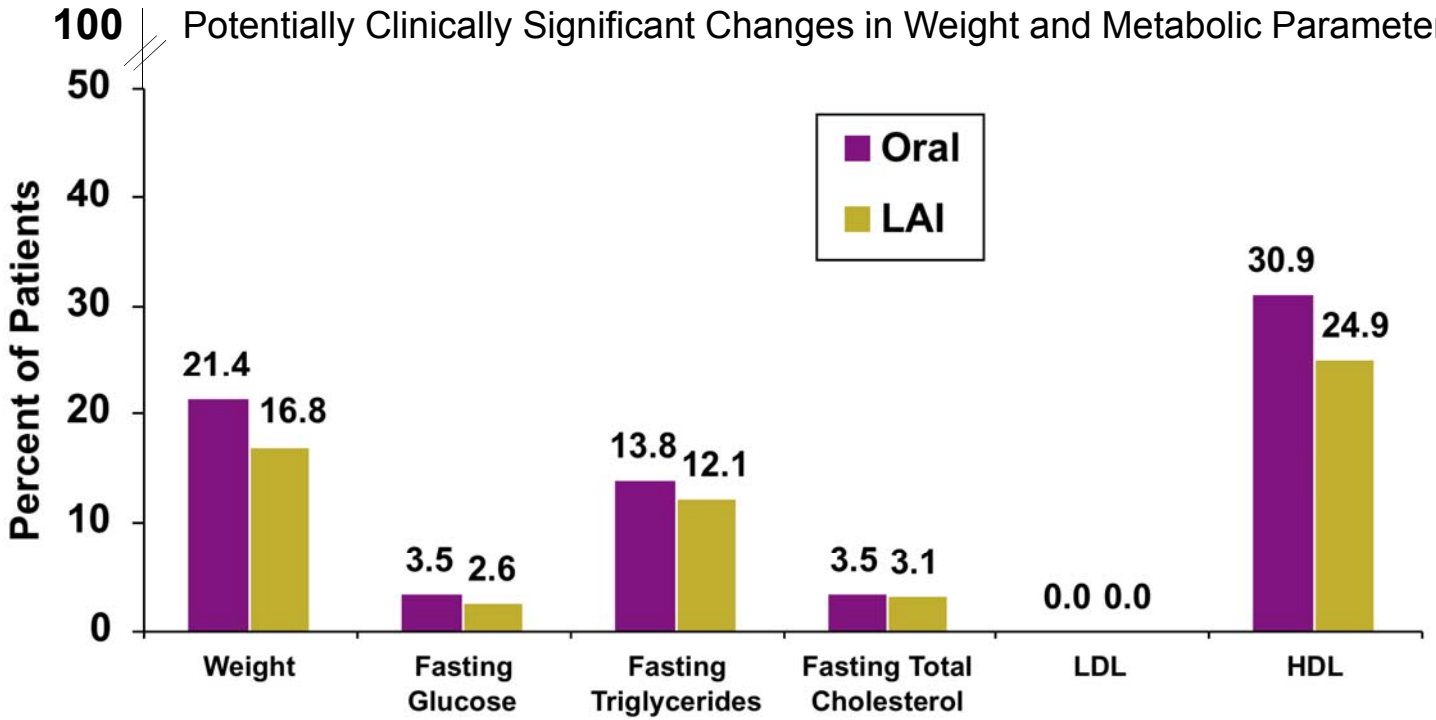
	ZYPADHERA %	Oral Olanzapine %
Patients with ≥1 TEAE	52.1	46.9
Weight Increased	7.2	7.5
Insomnia	7.2	4.0
Nasopharyngitis	4.3	4.3
Anxiety	4.8	2.8
Headache	3.2	4.3
Somnolence	3.8	2.8
Injection Site Pain	2.3	0.9
Hallucination	2.3	0.6

None of these events were statistically significantly different

AEs reported with ZYPADHERA were consistent with AEs reported with oral olanzapine, taking into account method of administration

McDonnell, et al. *Human Psychopharmacology.* 2011;26:422-433

Similar Metabolic Profile for ZYPADHERA and Oral Olanzapine Seen Over 24 Weeks

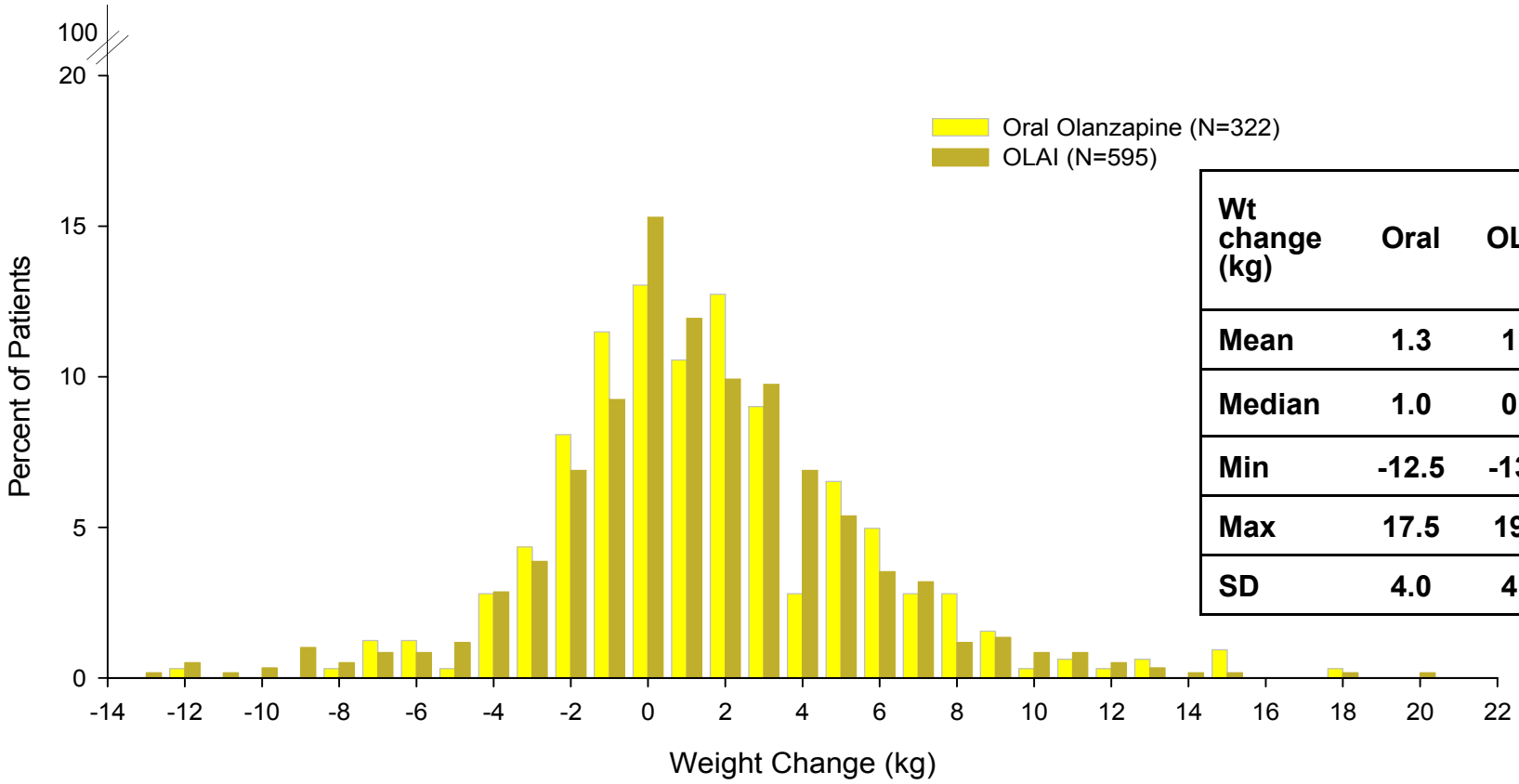


No significant differences between groups

PCS Definitions: weight, ≥7% change from baseline; fasting glucose, ≥7 mmol/L following baseline of <5.56 mmol/L; fasting triglycerides, ≥2.26 mmol/L following baseline of <1.69 mmol/L; total fasting cholesterol, ≥6.21 mmol/L following baseline of <5.17 mmol/L; fasting LDL, ≥4.13 mmol/L following baseline of <2.58 mmol/L; fasting HDL, <1.03 mmol/L following baseline of ≥1.03 mmol/L

McDonnell, et al. *Human Psychopharmacology.* 2011;26:422-433.

Similar weight change between ZYPADHERA and Oral Olanzapine over 24 wks



Wt change (kg)	Oral	OLAI
Mean	1.3	1.0
Median	1.0	0.7
Min	-12.5	-13.4
Max	17.5	19.5
SD	4.0	4.1

Note that baseline is after 4-8 wks on oral olanzapine. Mean weight gain during this lead in period was 1.06 kg.

OLAI = Olanzapine long-acting injection

McDonnell, et al. *Human Psychopharmacology.* 2011;26:422-433.

Dose Related Changes with ZYPADHERA

In a 24-week randomized, double-blind, fixed-dose study comparing 3 doses of ZYPADHERA in patients with schizophrenia, statistically significant differences among dose groups were observed for the safety outcomes below.

	ZYPADHERA Dose		
	150 mg/2 wk	405 mg/4 wk	300 mg/2 wk
Weight (kg)†	0.67	0.89	1.70*
Prolactin (μg/L)†	-5.61	-2.76	3.57*^
Fasting triglycerides‡	6.5%	9.8%	24.5%*^

†mean change
‡ change from normal at baseline to high at anytime (%)

*p<0.05 versus 150 mg/2 wk OP Depot
^p<0.05 versus 405 mg/4 wk OP Depot

FDA website, accessed 8 May 2013: http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4338s1-00-index.htm
Kane, Detke, Naber, et al. *Am J Psychiatry.* 2010;167:181-189.

Metabolic Monitoring

- ***Weight***
  - Weight gain ≥ 7% of baseline body weight was very common and ≥ 15% of baseline body weight was common following short-term treatment.
  - Weight gain ≥ 25% of baseline body weight was very common with long-term exposure.
  - **Weight should be monitored regularly,** e.g. at baseline, 4, 8 and 12 weeks after starting olanzapine and quarterly thereafter.
- ***Hyperglycemia and diabetes***
  - Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported uncommonly, including some fatal cases.
  - **Patients treated with any antipsychotic agents, including ZYPADHERA, should be observed for signs and symptoms of hyperglycaemia and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control**.
  - **Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines**, e.g. measuring of blood glucose at baseline, 12 weeks after starting olanzapine and annually thereafter.
- ***Lipid alterations***
  - Undesirable alterations in lipids have been observed in olanzapine-treated patients.
  - Lipid alterations should be managed as clinically appropriate.
  - **Patients treated with any antipsychotic agents, including ZYPADHERA, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines,** e.g. at baseline, 12 weeks after starting olanzapine and every 5 years thereafter.

For full prescribing information and complete safety profile, please see the ZYPADHERA SPC:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000890/WC500054429.pdf

Guidelines for Monitoring Patients Treated with Antipsychotics

Appropriate monitoring of weight, glucose, and lipids:

- ***Full details of appropriate monitoring*** **of patients treated with antipsychotics can be found in :**
  - Schizophrenia and Diabetes 2003' Expert Consensus Meeting, Dublin, 3–4 October 2003: consensus summary (distributed by Eli Lilly May 2009) . This is an example of a *national or locally utilised set of guidelines* for monitoring
    - Weight – Assess annually if patient established on an antipsychotic and at every visit for first 6 months if patient treatment naïve or switched from another antipsychotic. Provide lifestyle advice and refer to lifestyle management programme if available.
    - Glucose – Assess annually if established on an antipsychotic and at baseline and 3-6 months if patient treatment naïve or switched from another antipsychotic. Random or fasting glucose are acceptable and additional HBA1c testing may improve sensitivity and specificity. Refer to GP for definitive diagnosis if testing abnormal.
    - Lipids - Assess annually a full lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. Ideally sample taken after 9-12 hour fast. Refer to GP for definitive diagnosis and treatment if testing abnormal.
- **guidance on metabolic monitoring is also available from the American Diabetic Association or American Psychiatric Association guidelines**
  - http://professional.diabetes.org/CPR_search.aspx
  - http://www.psychiatryonline.com/pracGuide/pracGuideTopic_6.aspx

Metabolic and lifestyle issues and severe mental illness – new connections to well-being?
***J Psychopharmacol* 2005; 19(6) Supplement : 118-122**

Post Injection Syndrome Events in Pre-marketing Clinical Trials

In pre-marketing ZYPADHERA Clinical Trials:

- >2000 patients have received ZYPADHERA
- >50,000 injections have been given
- Post Injection Syndrome events occurred in 0.07% of injections (approximately 2% of patients)
  - In a clinic with 60 patients given 1 injection every 2 weeks, a 0.07% incidence would suggest that the clinic would see 1 event/year

Detke, McDonnell, Brunner, et al. *Int J Neuropsychopharmacol* 2010;13(suppl 1):244.
ZYPADHERA SPC: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000890/WC500054429.pdf

What is Post Injection Syndrome?

Also known as Post Injection Delirium/Sedation Syndrome

- Related to excessive olanzapine plasma concentrations
- Presentation consistent with many symptoms of oral olanzapine overdose
- Most commonly reported:
  - ***Delirium:*** including confusion, disorientation, agitation, anxiety or other cognitive impairment
  - ***Sedation***: ranging from mild in severity up to coma (lasting up to 12 hrs in one case)
- Other symptoms may include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension or convulsions
- Typically begins with milder symptoms which progress in severity and/or number
- Presentation can appear similar to alcohol intoxication

Time of Onset of Symptoms	Patients
<60 minutes	~80%
1 to 3 hours	~ 20%
>3 hours	<5%

Detke, McDonnell, Brunner et al. *BMC Psychiatry* 2010;10:43.

Clinical Manifestations of Post Injection Syndrome

Symptom Groups (N=30 cases)	Presented Initially %	Occurred at Any Time %
Sedation (somnolence, sedation, unconsciousness)	40	87
Delirium (combined)	47	97
Speech impairment (dysarthria)	23	70
Motor impairment (ataxia)	23	40
Cognitive impairment (confusion, disorientation)	27	57
EPS, akathisia, tension, or cramps in extremities	10	23
Agitation, aggression, irritability, anxiety, restlessness[a]	7	30
General malaise (weak, dizzy, felt bad)	63	67
Hypertension	3	7
Possible seizures/convulsions	0	7

Abbreviations: EPS = extrapyramidal symptoms

[a] Restlessness may also be a manifestation of EPS (akathisia)

Detke, McDonnell, Brunner, et al. *BMC Psychiatry* 2010; 10:43.

Medical Status and Recovery

In patients experiencing Post Injection Syndrome Events:

- No clinically significant decreases in blood pressure noted
- No respiratory depression noted
- Some patients experienced temporary unconsciousness (23%)
- Most patients were hospitalized for further observation and/or treatment (77%)
- Two patients were intubated prophylactically following parenteral administration of benzodiazepines (No respiratory depression noted)
- Concomitant medications/substances have not been shown to be risk factors

Recovery in patients experiencing Post Injection Syndrome Events:

- All patients have fully recovered with no lingering or apparent permanent sequelae
- Time to full recovery was between 1.5 and 72 hours
- Approximately 70% of patients continued to receive ZYPADHERA injections

Detke, McDonnell, Brunner, et al. *BMC Psychiatry* 2010; 10:43.

Possible Causality or Mechanism and Injection Safety Precautions

- **Possible Causality or Mechanism of Post Injection Syndrome Events**
  - ZYPADHERA is more soluble in blood than muscle
  - Contact with a substantial volume of blood results in more "rapid release" of a portion of the dose, possibly resulting from
    - Partial injection into vasculature
    - Significant vessel injury during IM injection (nick or puncture)
    - Substantial bleeding at injection site
- **Injection Safety Precautions**
  - Post Injection Syndrome risk is present with each injection of ZYPADHERA
  - Good injection technique is important
    - Intended for deep intramuscular gluteal injection
      - Not for intravenous, subcutaneous, or deltoid injection
    - Aspirate syringe prior to injection to ensure no blood is visible

McDonnell, Detke, Bergstrom, et al. *BMC Psychiatry* 2010;10:45.

Clinical Management and Subsequent Antipsychotic Treatment

Management of Post Injection Syndrome Events

- Treat symptomatically
- Continue close medical supervision and monitoring until symptoms have resolved
- If parenteral benzodiazepines are essential for management of post-injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended

Following a Post Injection Syndrome Event

- If treatment with ZYPADHERA is continued
  - The next injection may occur as previously scheduled or earlier if clinically indicated for exacerbation of symptoms
  - Temporary oral supplementation may be considered
- If ZYPADHERA is discontinued
  - The treatment effects of ZYPADHERA will continue for some time after discontinuation (Half life is approximately 30 days)
  - Treatment with alternative medication may be started when clinically indicated

Safety Precautions

With each ZYPADHERA injection —

After the injection:

- Patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours.
  - The patient should be located where he can be seen and/or heard.
  - At least hourly checks for signs of a post injection syndrome event are recommended.

Immediately prior to leaving the healthcare facility:

- Confirm that the patient is alert, oriented, and absent of any signs or symptoms of overdose
  - If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved.
  - The 3 hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose.
- Advise patients to be vigilant for symptoms of a post injection syndrome event for the remainder of the day and be able to obtain assistance if needed.

After leaving the healthcare facility:

- Patients should not drive or operate machinery for the remainder of day.

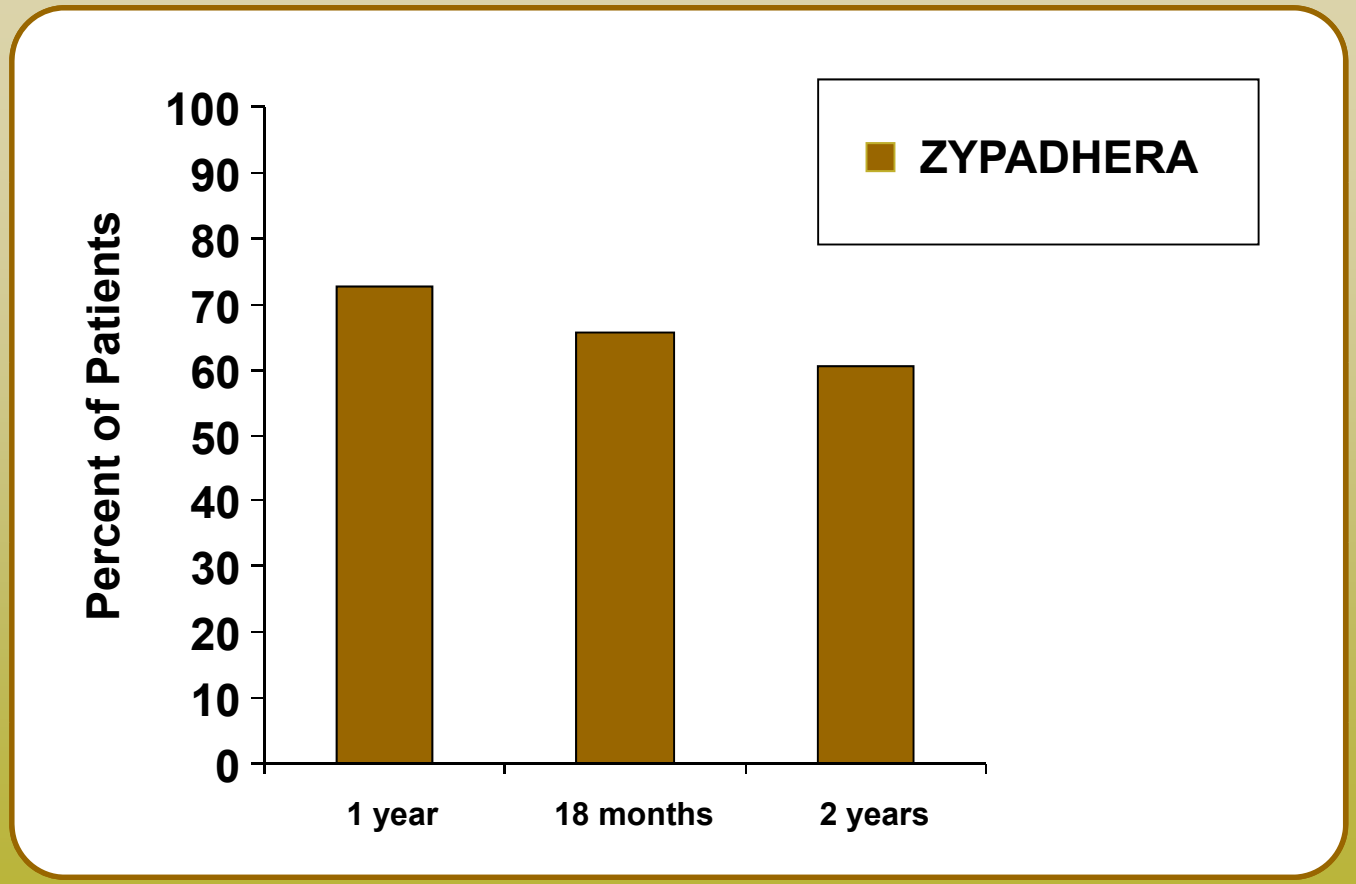
Detke, McDonnell, Brunner, et al. *BMC Psychiatry* 2010; 10:43.
ZYPADHERA SPC: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000890/WC500054429.pdf

Weighing Benefits/Risks of ZYPADHERA

Benefits	Risks
▪ Proven efficacy in schizophrenia ▪ No oral supplementation required ▪ Flexible 2 to 4 week dosing options	▪ Adverse event profile similar to oral Zyprexa treatment, except for injection-related events ▪ Post Injection Syndrome events ▪ Observation period and precautions

Weigh overall safety profile against the potential benefits in the patient with schizophrenia who needs a long-acting injection

66% of Patients Continuing Treatment with ZYPADHERA at 18 months



McDonnell, et al. *Clin Med Insights: Psychiatry* 2011; 3:37-47.
FDA website, accessed 8 May 2013: http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4338s1-00-index.htm

Considerations for Use of ZYPADHERA

How might you appropriately and efficiently manage the safety considerations to enable your patients to realize the potential benefits of ZYPADHERA?

Benefits of ZYPADHERA

Safety profile and risk management

Reporting adverse events: ADR Reporting, website: www.medicinesauthority.gov.mt/adrportal