Psychiatry: An Innovative Drug Discovery Pipeline

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Psychiatric disorders: A major worldwide burden

7 of top 20 WHO causes of disability in 2030

2	Unipolar depression
8	Alcohol use disorders
9	Schizophrenia
10	Self inflicted injuries
11	Bipolar disorder
18	Drug use disorders
19	Panic disorder

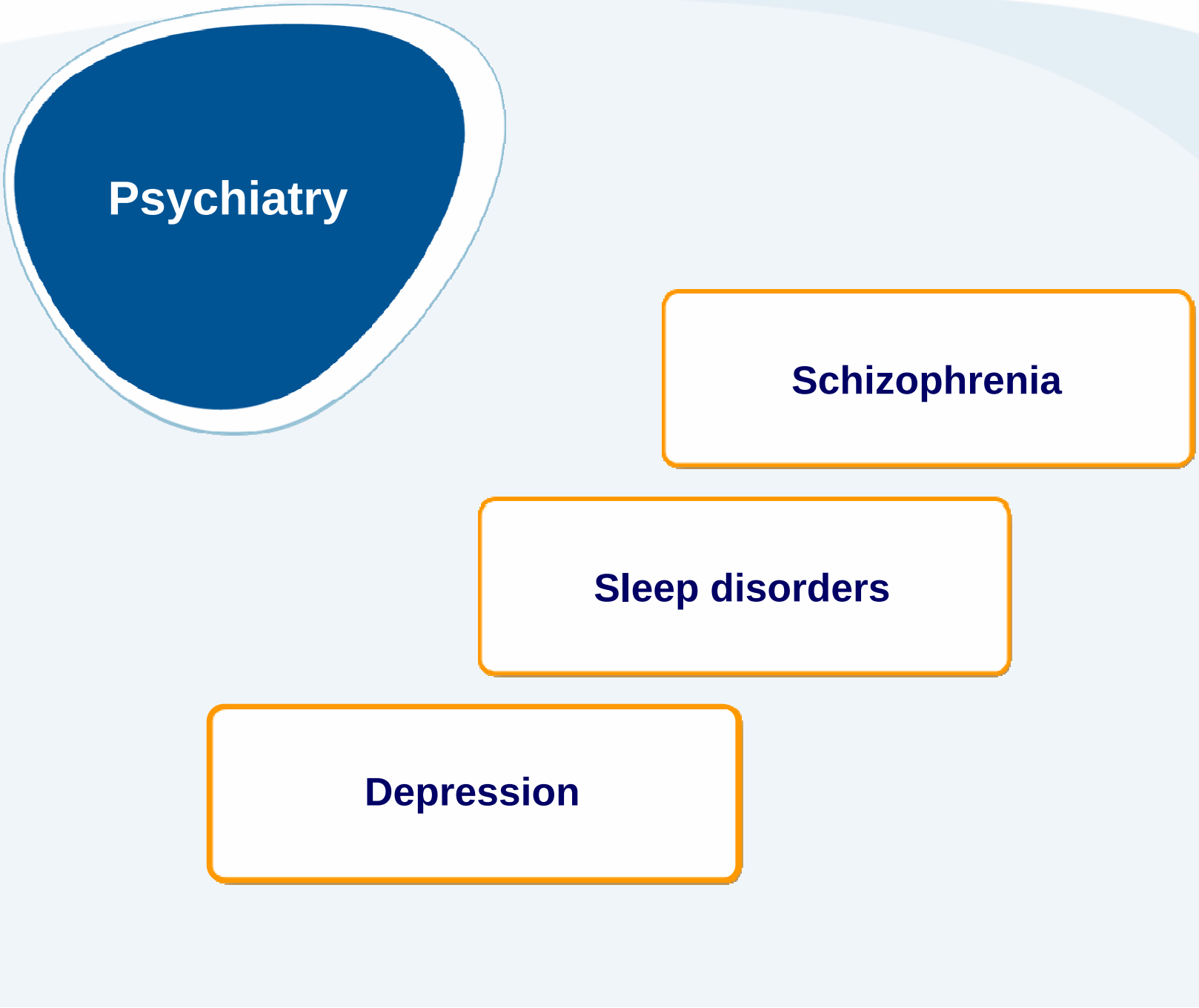
- Chronic and life long diseases
- Debilitating
- Huge societal cost
- Poorly treated

WHO – Global Burden of Disease - Leading causes of disability in DALYs estimate for 2030
Colin D. Mathers, Dejan Loncar - Updated Projections at January 2006

Innovative and competitive drug discovery pipeline

	Phase I	Phase II
DEPRESSION & ANXIETY	pan 5HT1 ant 163090 NK1 ant Orvepitant NK1 ant/SSRI 424887 CRF1 ant 561679†	5HT/NE/DA rui 372475† CRF1 ant 876008† P38 inh 856553
SCHIZOPHRENIA	GlyT1 inh 1018921 AMPA + mod 729327 H3 ant 239512	DA/5HT ant 773812
SLEEP DISORDERS		Orexin ant 649868†
BIPOLAR DISORDER	NaChBlk 1014802	
DEPENDENCE & COMPULSIVITY	D3 ant 598809	Gly ant 468816

† collaboration (‘475 with Neurosearch, ‘679 & ‘008 with Neurocrine, ‘868 with HGS)


Psychiatry
Schizophrenia
Sleep disorders
Depression

Schizophrenia

Sleep disorders

Depression

multiple innovative mechanisms

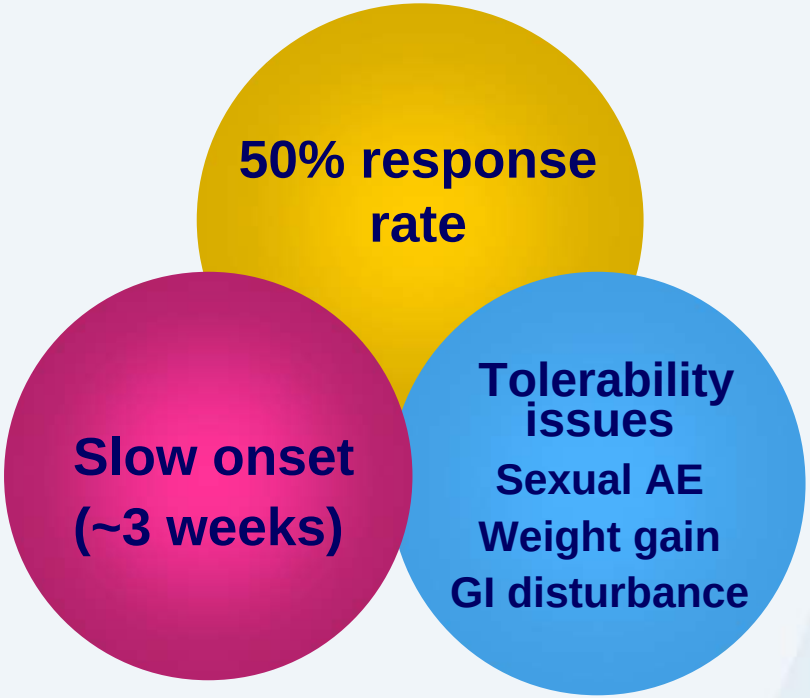
Depressive disorders:
The 2nd largest burden of disability

Multiple domains affected: Mood, Pleasure, Cognition, Alertness

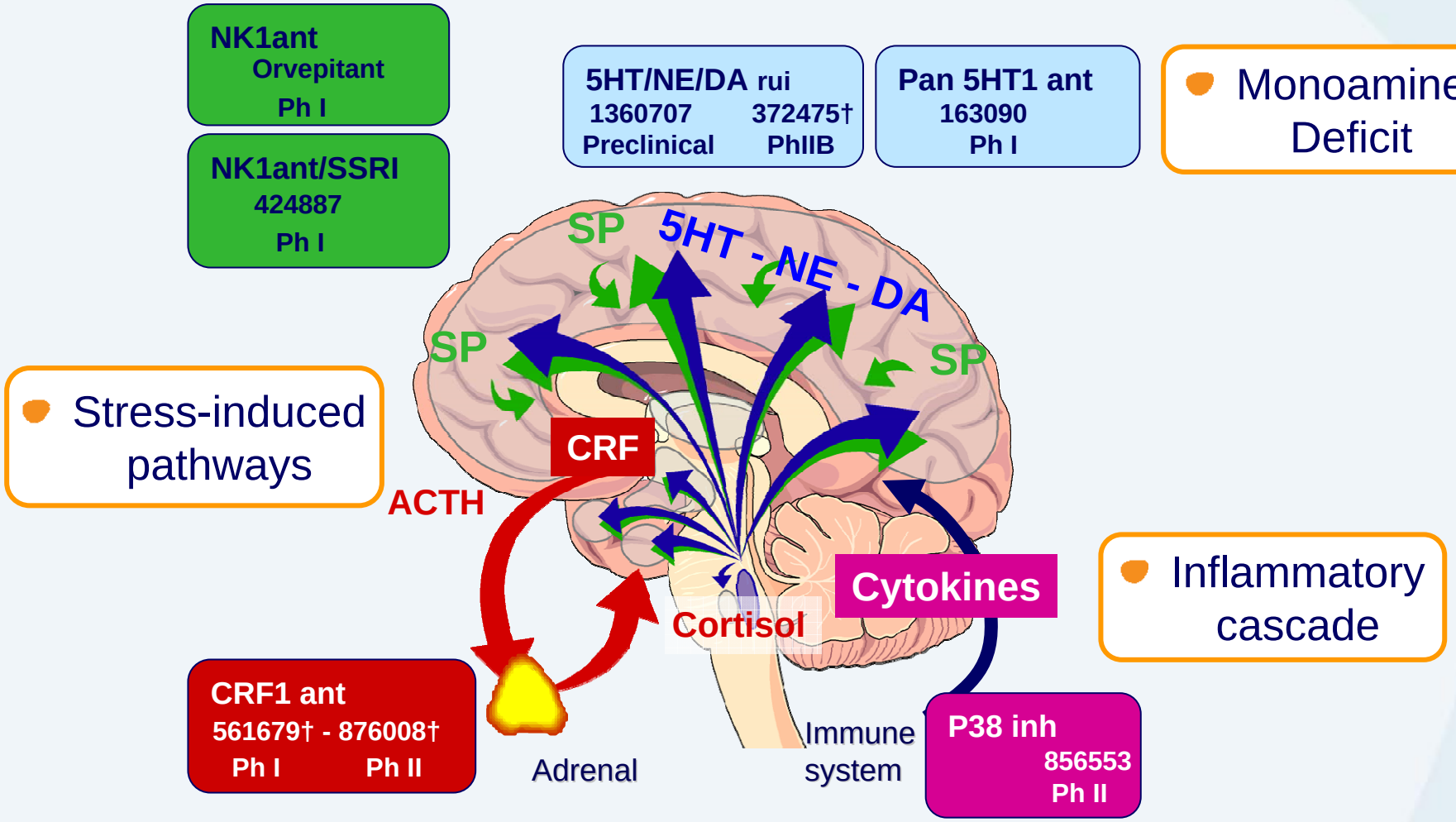
Unmet Needs

- More effective treatment
- Faster Onset
- Better Tolerability

Current Treatments

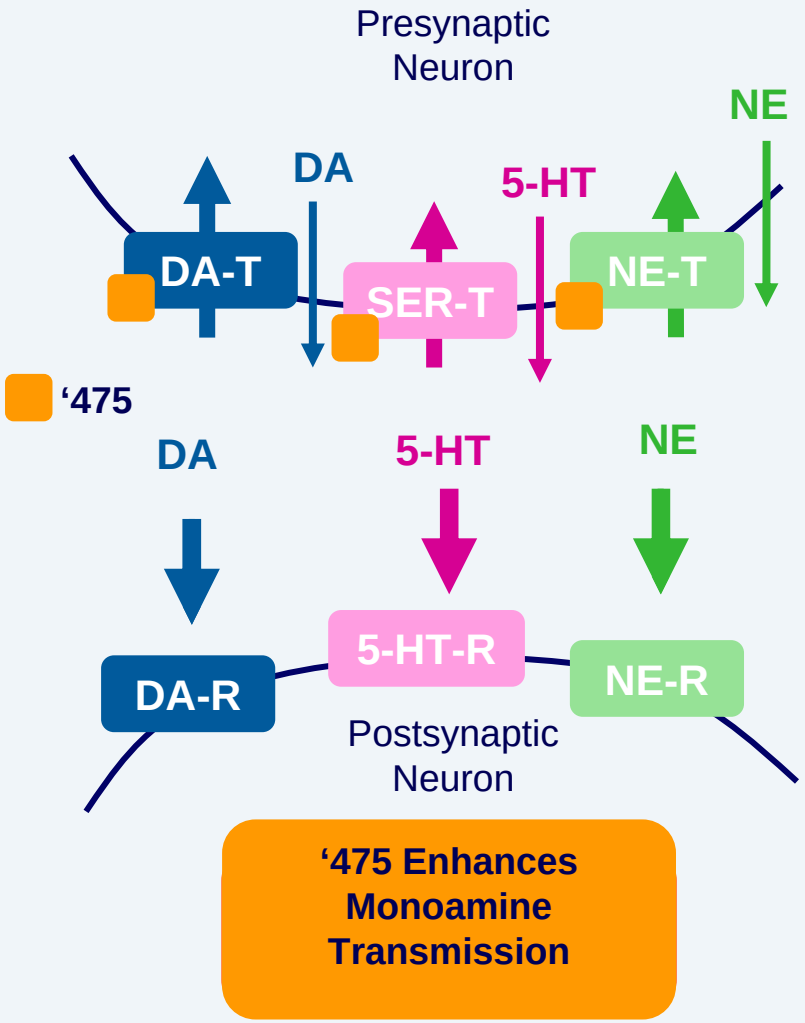


The pathology of depression



† collaboration (‘475 with Neurosearch, ‘679 & ‘008 with Neurocrine)

‘475: Capturing the full potential of the three monoaminergic systems



‘475 Triple Reuptake Inhibitor

- **Equipotent on all 3 human transporters**
- **Increases synaptic monoamines: 5-HT, NA, DA**
- **Lacks side effects of SSRIs and SNRIs**
- **Enhances cognitive performance**

In-licensed from Neurosearch

‘475: Favourable safety and tolerability

3 Phase I studies completed

- 210 subjects treated
- Well tolerated
- No clinically significant changes in vital signs or ECG

- PET Receptor Occupancy
  - DAT = 60-80%
  - SERT = 55-75%

  At 1-2 mg (well tolerated doses)

In-licensed from Neurosearch

Two phase IIB studies ongoing

Moderate to severely depressed patients

Primary endpoints: antidepressant efficacy versus placebo

Secondary endpoints: safety and tolerability

‘475 (low to medium dose)	‘475 (medium to high dose)
Placebo	Placebo
paroxetine	venlafaxine
n = 465	n = 378

Phase IIB due to complete in 1H 2009

In-licensed from Neurosearch

Schizophrenia

Sleep disorders

a promising novel approach to insomnia

Depression

‘868: Phase II study design in insomnia

Primary Insomnia Patients

Primary endpoints: LPS, TST, WASO by Polysomnography

Secondary endpoints: subjective sleep, safety and tolerability

2 day Crossover Study

- **‘868 10mg**
- **‘868 30mg**
- **‘868 60mg**
- **Placebo**

n = 52

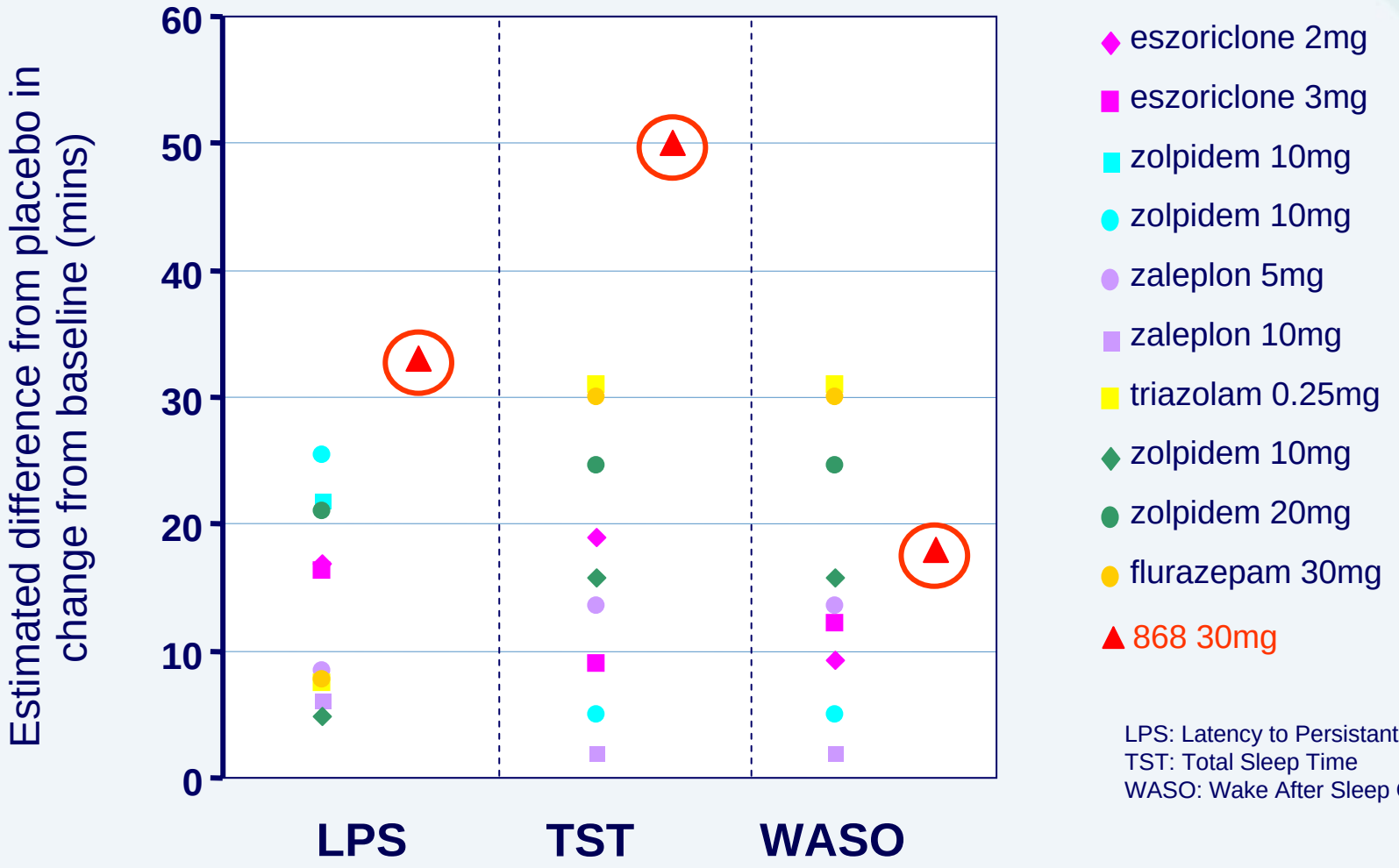
LPS: Latency to Persistant Sleep
TST: Total Sleep Time
WASO: Wake After Sleep Onset

Preclinical tox finding being addressed

Agreement with HGS

‘868: Efficacy versus marketed hypnotics

Not comparative data



LPS: Latency to Persistant Sleep
TST: Total Sleep Time
WASO: Wake After Sleep Onset

Agreement with HGS

Schizophrenia

addressing the pathophysiology with mono and add-on therapy

Sleep Disorders

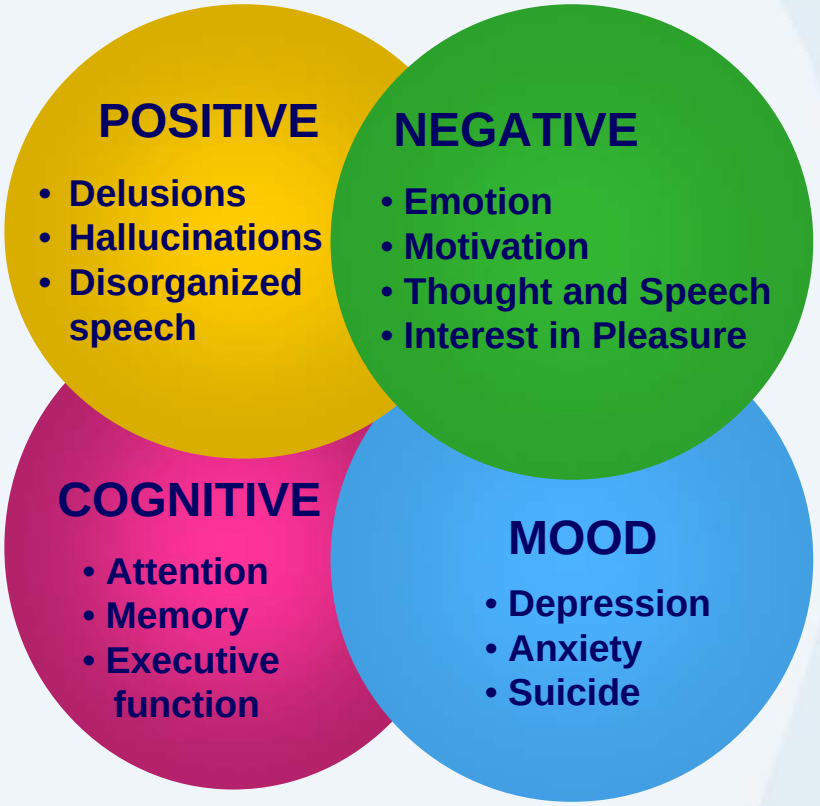
Depression

Schizophrenia:
The most devastating psychiatric disease

Unmet Needs

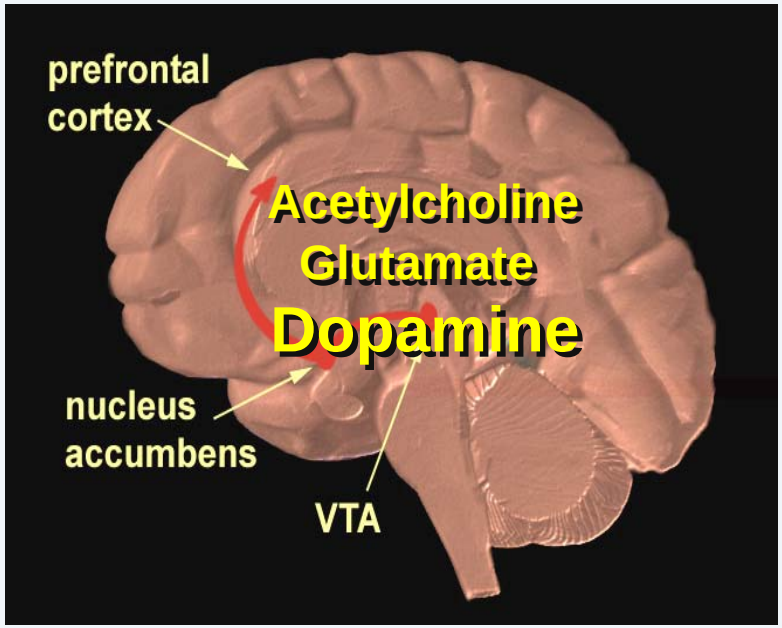
- Positive symptoms in treatment refractory patients
- Negative symptoms
- Depression and anxiety
- **Cognitive symptoms**
- **Better tolerability**

Multiple symptoms



Multiple approaches to treat Schizophrenia domains

- Cholinergic Hypofunction



Monotherapy

Positive, Negative & Cognitive symptoms

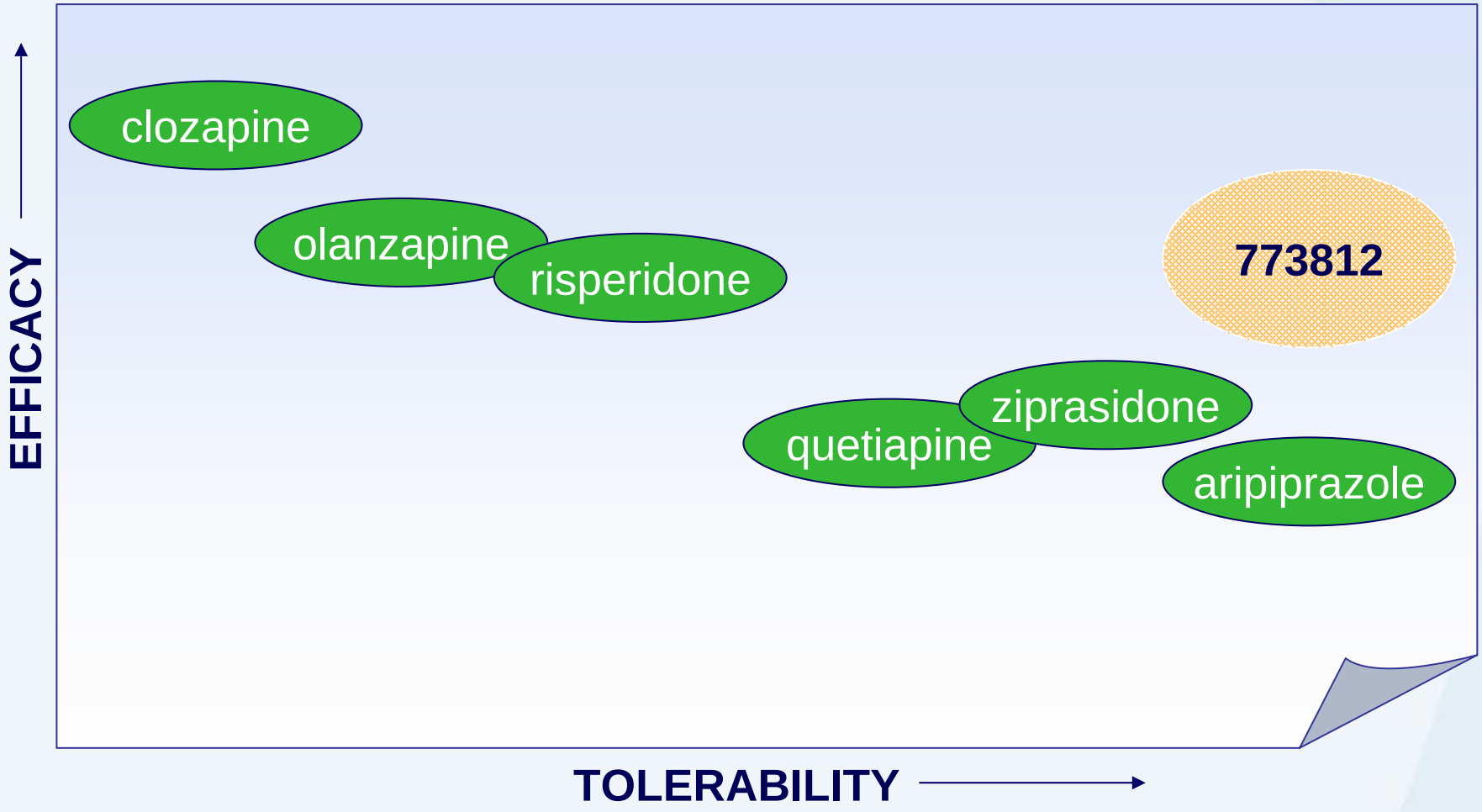
- **DA/5HT antag**
  773812
  Ph IIb
- **GlyT1 inh**
  1018921
  Ph I
- **M1 agonist**
  1034702
  Preclinical

Add–on Therapy

Cognitive symptoms

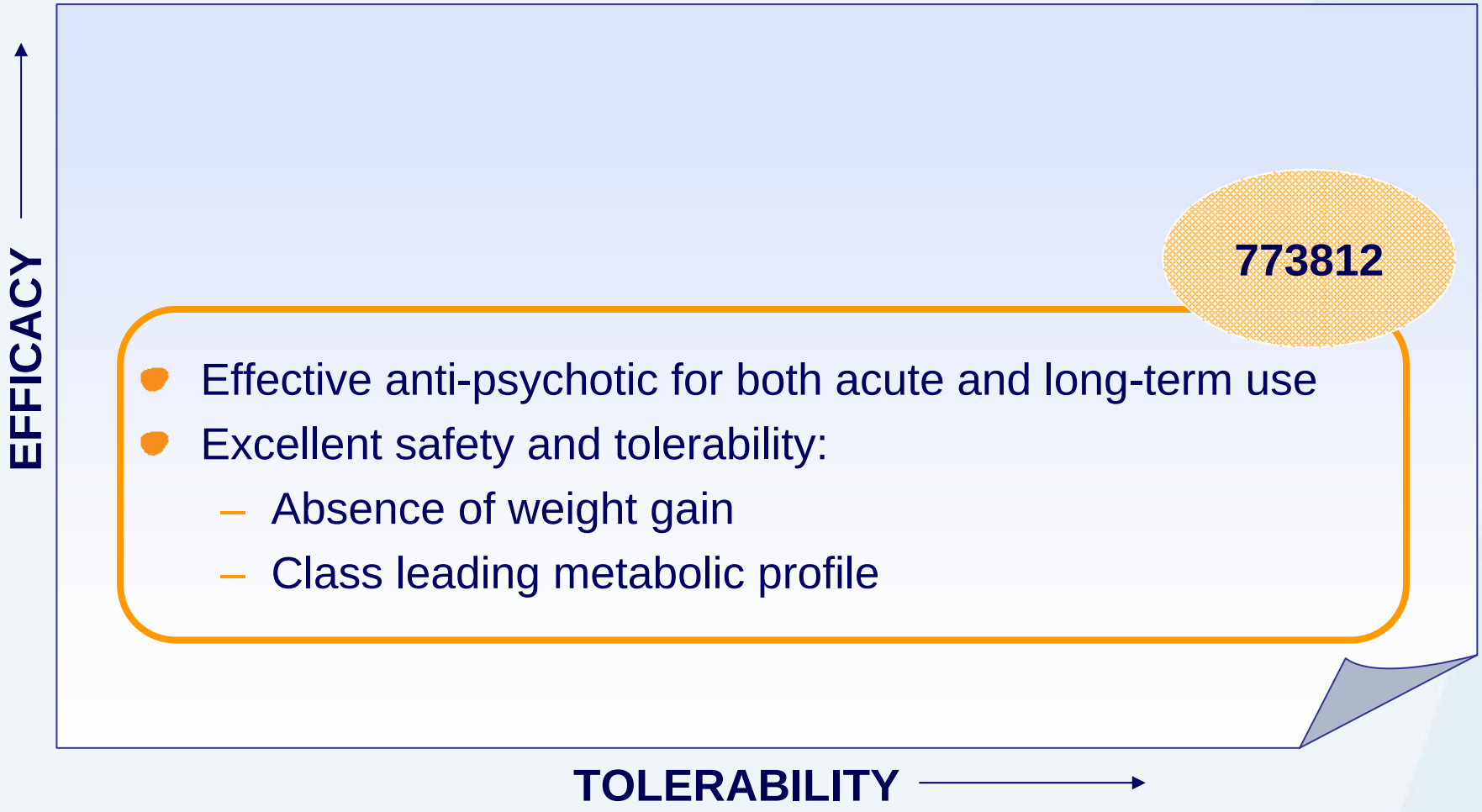
- **AMPA +ve mod**
  729327
  Ph I
- **H3 antagonist**
  239512
  Ph I

Atypical antipsychotics: The opportunity with ‘812



Source: GSK market research – Physician perceptions

Atypical antipsychotics: The opportunity with ‘812



Atypical antipsychotics & metabolic syndrome risk

Atypical Antipsychotic Metabolic related effects:

- Weight gain
- Glucose intolerance
- Insulin resistance
- Dyslipidaemia
- Type II Diabetes

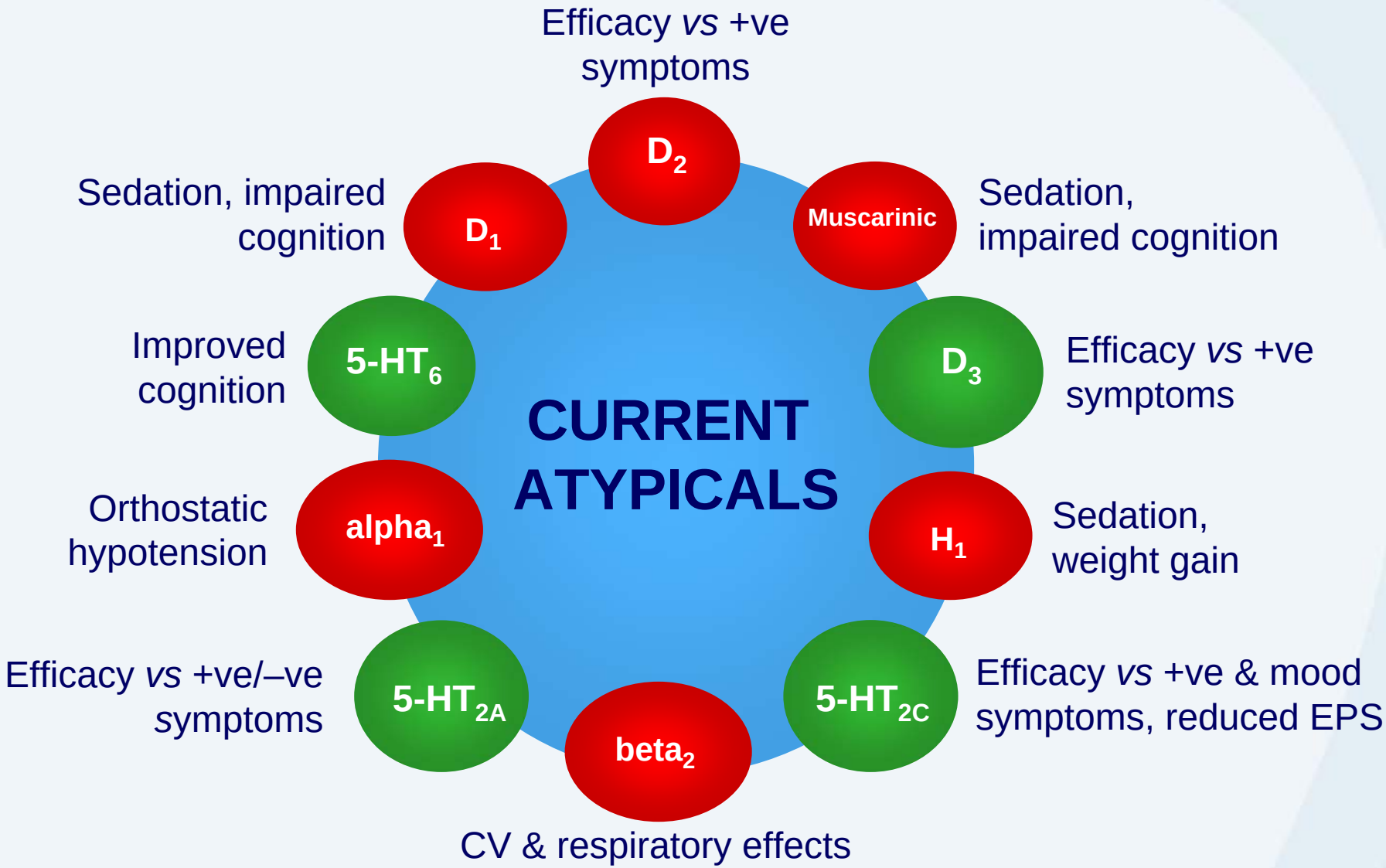
Metabolic Data from CATIE Phase 1			
Agent	Weight[1] (%)	Triglyceride[2] (mg/dl)	Cholesterol[3] (mg/dl)
Olanzapine	30	+43	+8.5
Quetiapine	16	+19	+3.5
Risperidone	14	-2.6	-3.0
Ziprasidone	7	-18	-1.0
Perphenazine	12	-18	-1.0

[1] % individuals who gained >7% of their baseline body weight
[2] Mean change in triglyderide level
[3] Mean change in total cholesterol levels

Source: The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) N Engl J Med 2005, 353(12):1209-1223

Need for new drugs with clean metabolic profile

‘812…better Antipsychotic by rational design



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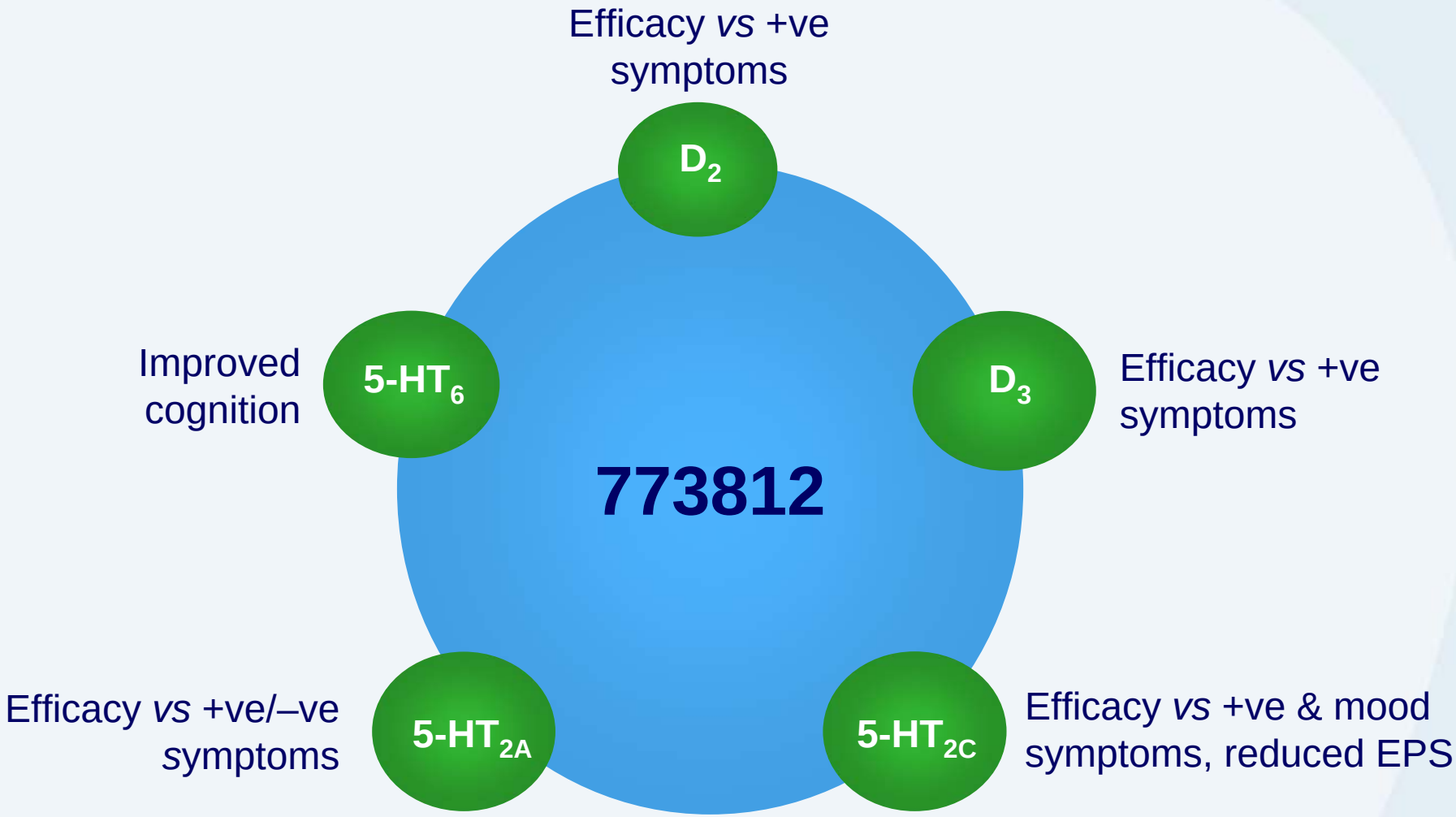


Phase II study design

Schizophrenic patients in acute exacerbation phase

Primary endpoints: PANSS Total
Secondary endpoints: safety and tolerability

6 weeks study

- ‘812 60mg
- ‘812 120mg
- olanzapine 15mg
- Placebo

n = 217

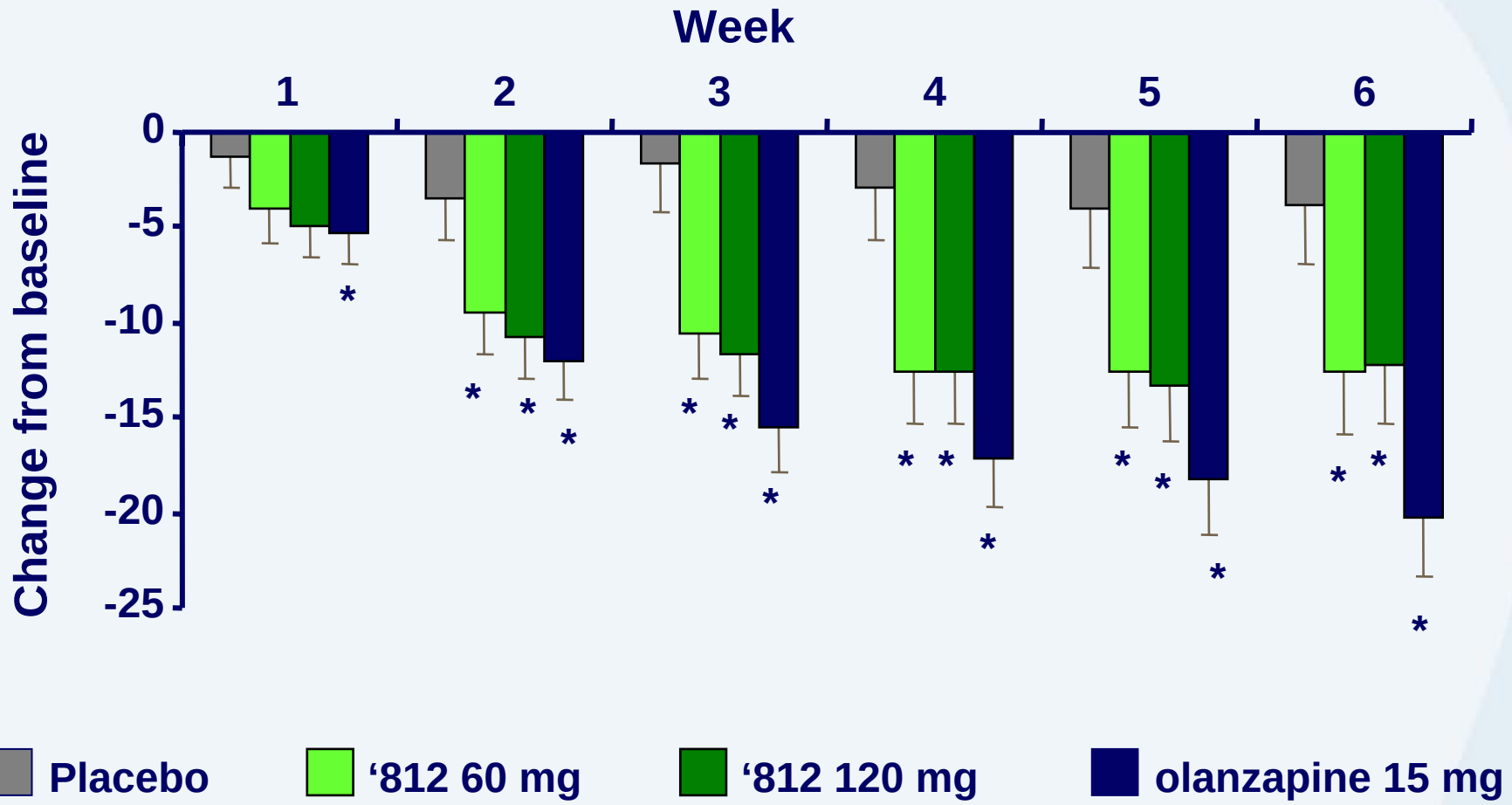
12 weeks study

- ‘812 60mg
- olanzapine 15mg
- Placebo

n = 101

Evidence of clinical efficacy at week 6

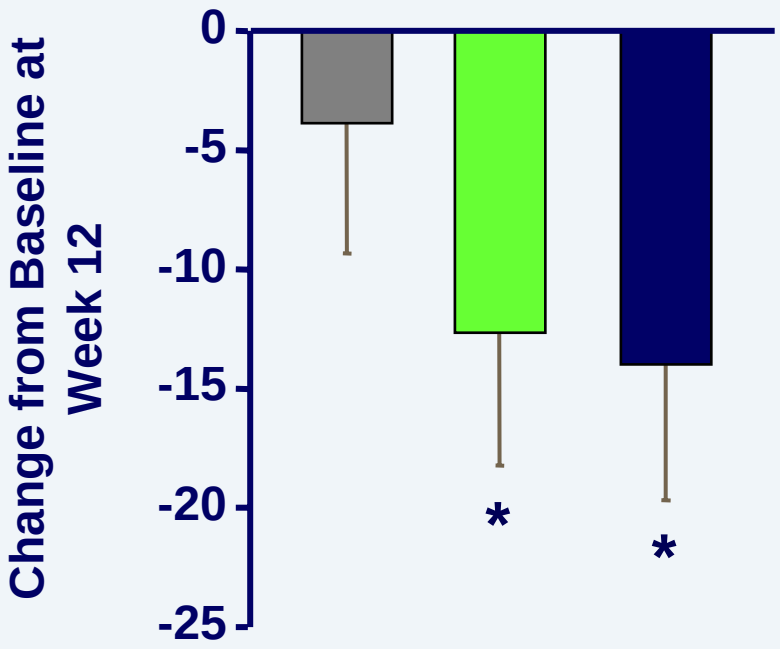
Change from baseline in PANSS Total



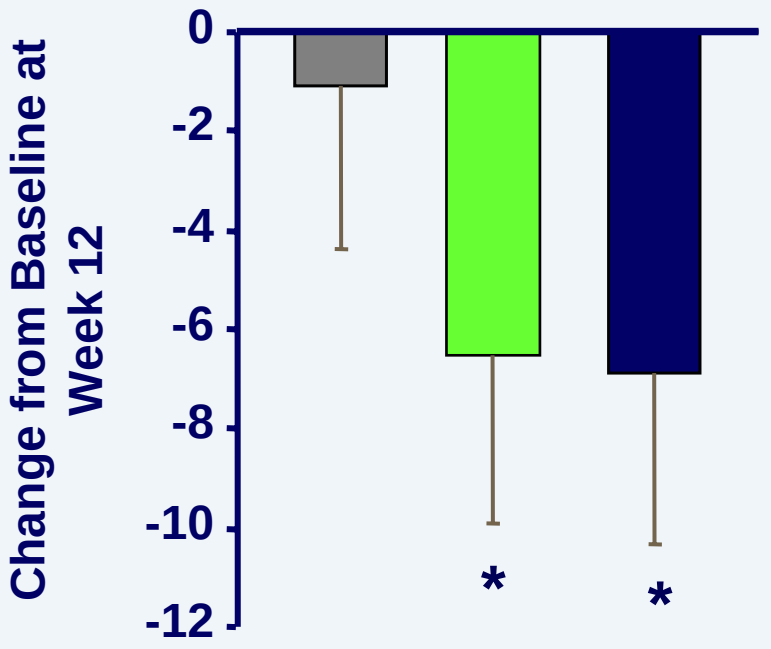
Difference from placebo: * p<0.05

….and at week 12

PANSS Total score



BPRS Total score

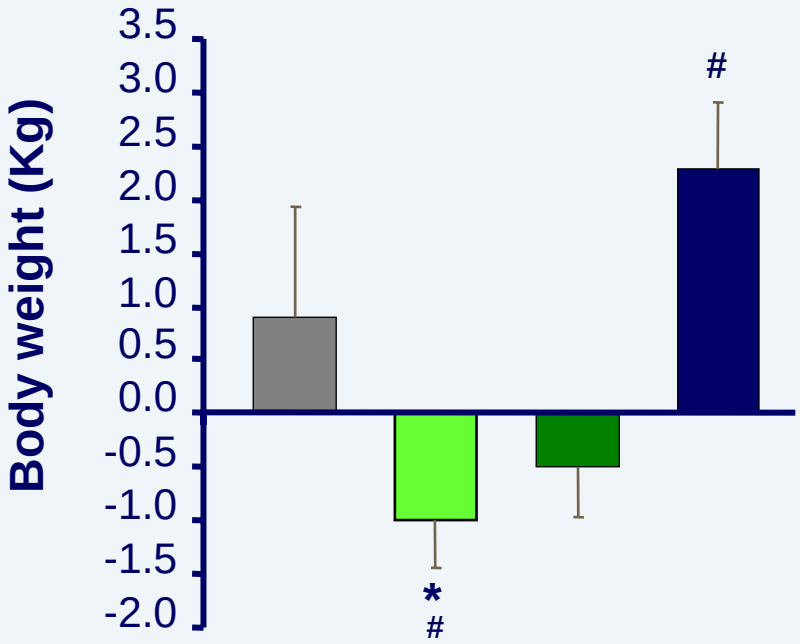


Placebo ‘812 60 mg olanzapine 15 mg

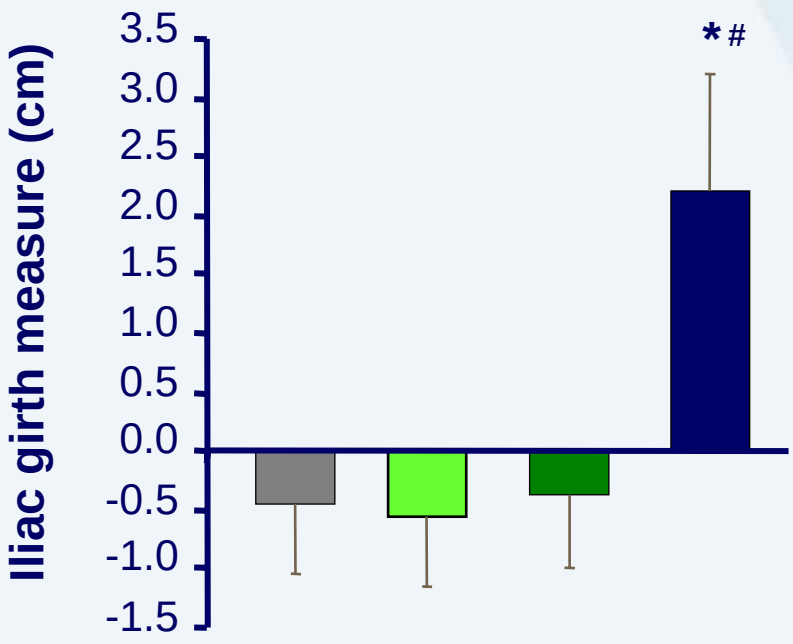
Difference from placebo: * p<0.05

‘812: Advantageous body weight profile

Body Weight



Girth



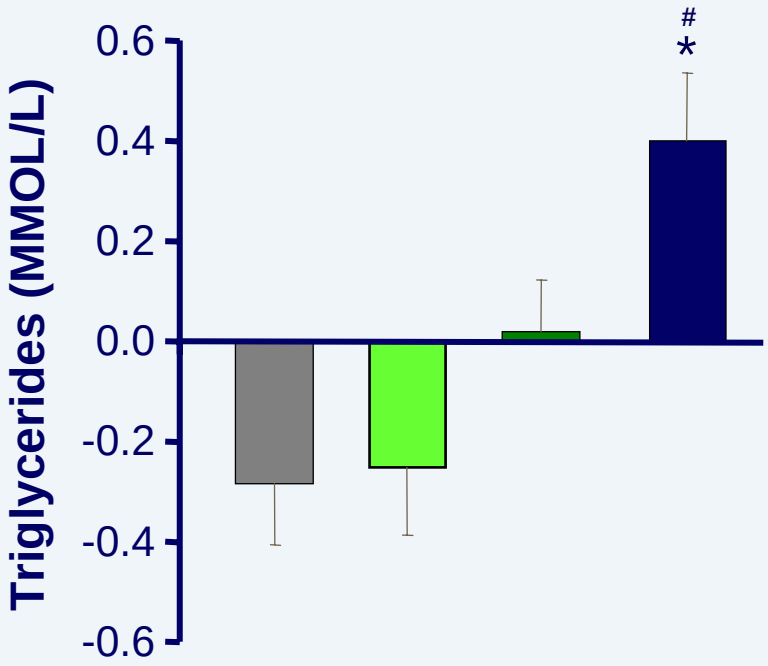
Change from Baseline at Week 6

Placebo **‘812 60 mg** **‘812 120 mg** **olanzapine 15 mg**

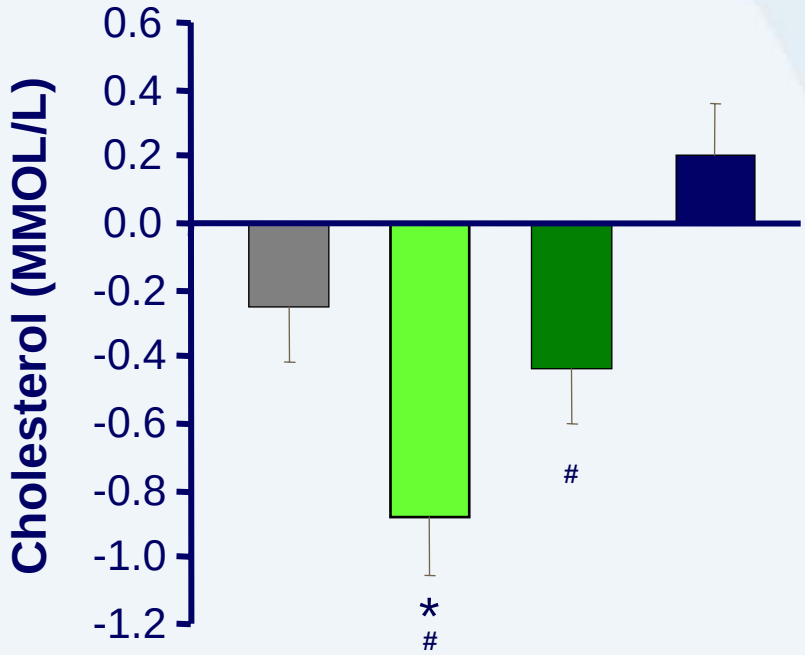
Difference from placebo: * p<0.05
Difference from baseline: # p<0.05

….and advantageous lipid profile

Triglycerides



Cholesterol



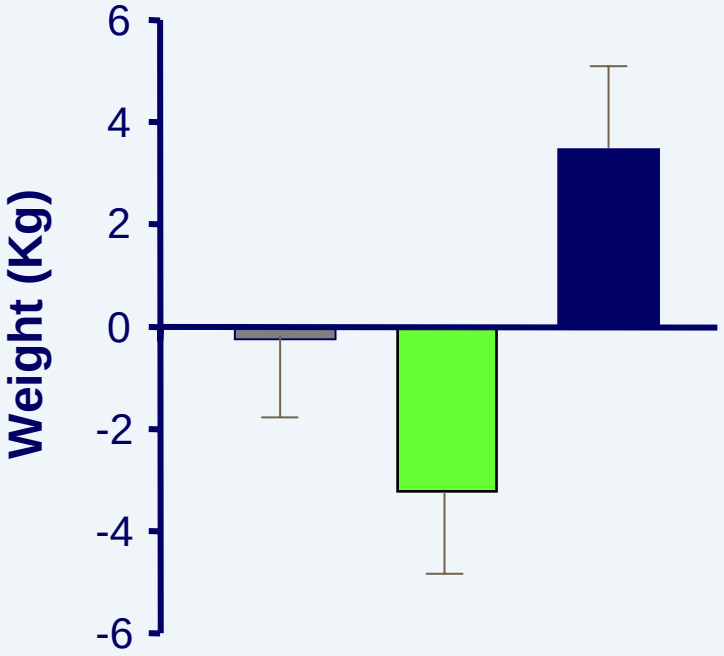
Change from Baseline at Week 6

Placebo **‘812 60 mg** **‘812 120 mg** **olanzapine 15 mg**

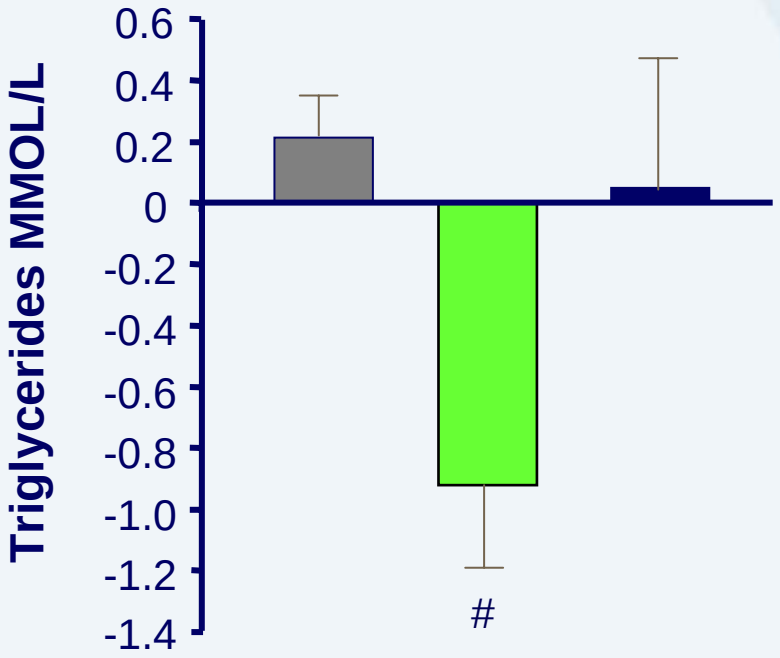
Difference from placebo: * p<0.05
Difference from baseline: # p<0.05

‘812: Advantageous metabolic profile at week 12

Body weight



Triglycerides



Change from Baseline at Week 12

Placebo **‘812 60 mg** **olanzapine 15 mg**

Difference from baseline: # p<0.05

‘812: Opportunity and next steps

- Promising efficacy data
- Favourable metabolic profile
- Good tolerability

Phase IIB programme to start in 1H 2008


gsk
GlaxoSmithKline