

NOVEL INDICATIONS:

Experiences from a Study in MDD with
Mixed Features (Mixed Depression)

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Disclosures

I am a full time employee of Sunovion
Pharmaceuticals

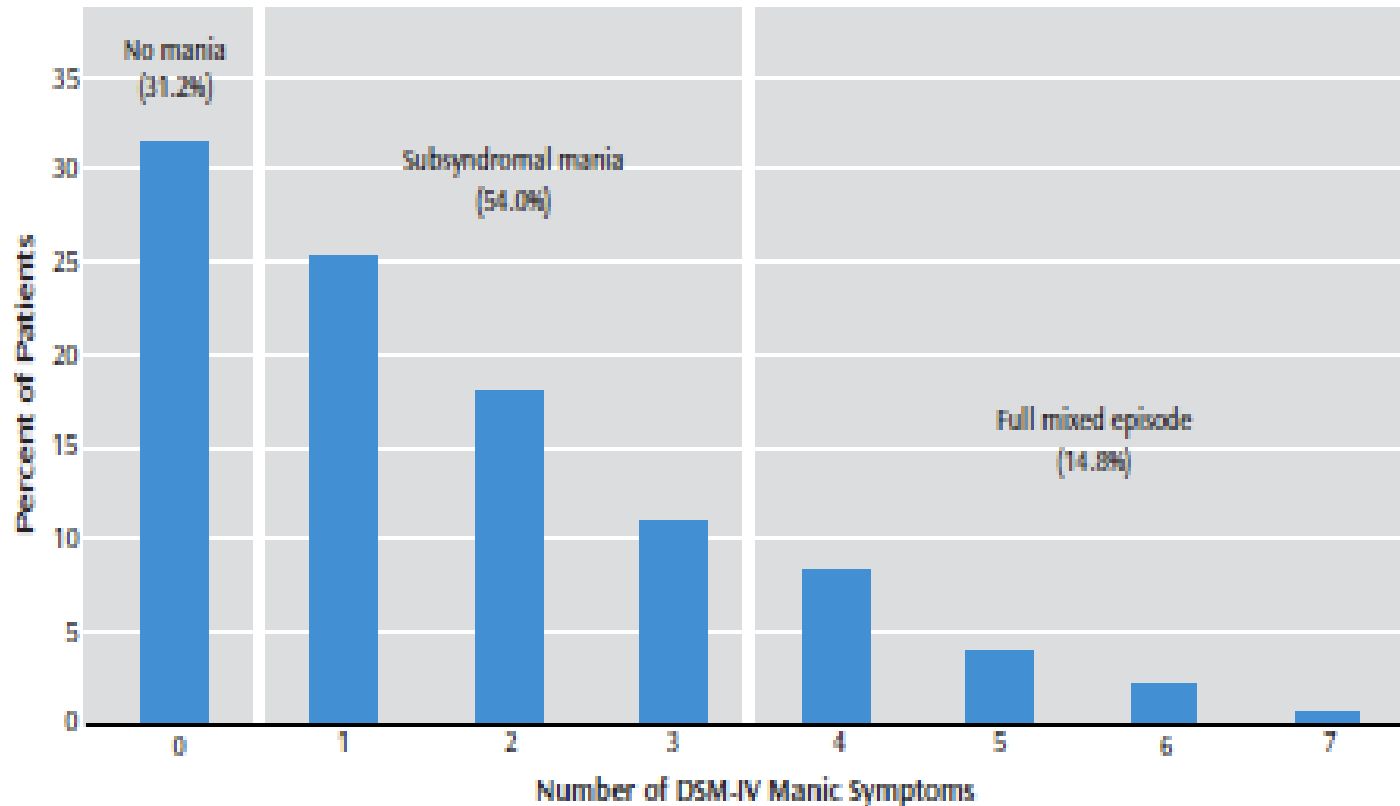
Overview

1. MDD with mixed features (mixed depression)
2. Lurasidone development programs have provided insight into potential new indications
 - PEARL schizophrenia
 - PREVAIL bipolar depression
3. RESOLVE Study in mixed depression
 - Definition and characterization of the diagnosis
 - Baseline characteristics of enrolled patients

WHAT IS MIXED DEPRESSION?

The majority of bipolar depressive episodes have symptoms of mania

Number of DSM-IV Manic Symptoms During an Index Episode of Bipolar Depression in STEP-BD (N=1,380)



Epidemiology of Mixed Depression

- Large-scale studies have confirmed high rates of concomitant sub-syndromal hypomania among MDD population (~40-50%) (*P. Zimmerman et al., Arch.Gen Psych. 2009; T. Suppes et al. Arch. Gen Psych 2005; J. Angst et al. AJP 2010; J. Goldberg et al., Am J Psych 2009, Benazzi et al., 2007, 2008; M. Frye et al., Am J Psych 2009; Benazzi and Akiskal, 2006*)
- Prevalence of mixed depression (7-9%) approaches that observed for MDD alone (10%) (*J. Angst et al. AJP 2010; P. Zimmerman et al., Arch.Gen Psych. 2009*)
- Compared with MDD patients, mixed depression patients display higher rates of comorbidity with:
 - Substance abuse disorders (*P. Zimmerman et al., Arch.Gen Psych. 2009; Dodd et al., J Aff Dis 2010*)
 - Behavioral problems and criminal acts (*P. Zimmerman et al., Arch.Gen Psych. 2009; Angst et al., 2010*)
 - Panic disorder (*Zimmerman et al., 2009*)
 - Suicidality (*Balazs et al., 2006; Angst et al., 2010; Goldberg et al., 1998; Judd and Akiskal, 2003*)
 - Overrepresented in women (*Suppes et al., 2005, Akiskal and Benazzi, 2003*)
- Associated with poorer long-term clinical outcomes compared with pure MDD (*Dodd et al., 2010, Angst et al., 2010*)

DSM-5:

Major Depressive Episode With Mixed Features

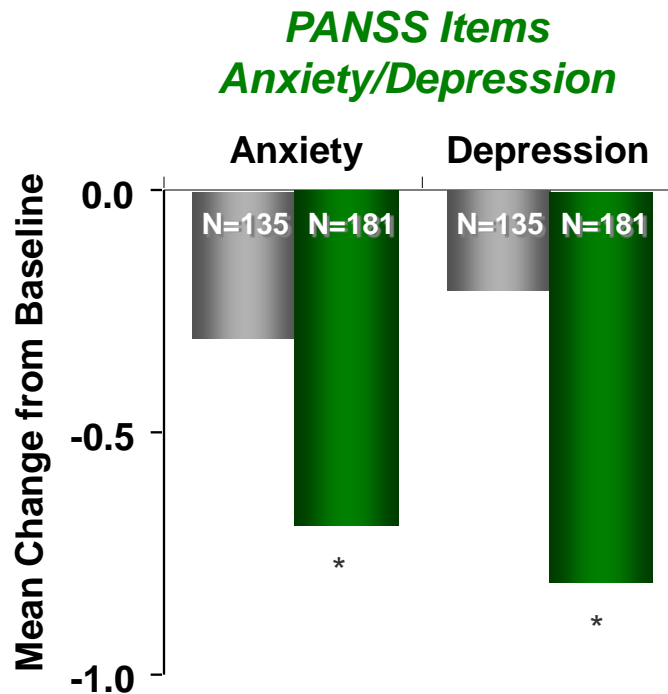
- Full criteria for a major depressive episode and **at least 3** of the following symptoms are present nearly every day during the episode:
 - Elevated, expansive mood
 - Inflated self-esteem or grandiosity
 - Flight of ideas or subjective experience that thoughts are racing
 - More talkative than usual or pressure to keep talking
 - Increase in energy or goal-directed activity (either socially, at work or school, or sexually)
 - Increased or excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
 - Decreased need for sleep (feeling rested despite sleeping less than usual [to be contrasted from insomnia])
- Symptoms of mood elevation excluded from core defining symptoms:
 - Irritability, psychomotor agitation, distractibility, insomnia

Translational evidence from late phase studies – Can this be achieved?

Considerations:

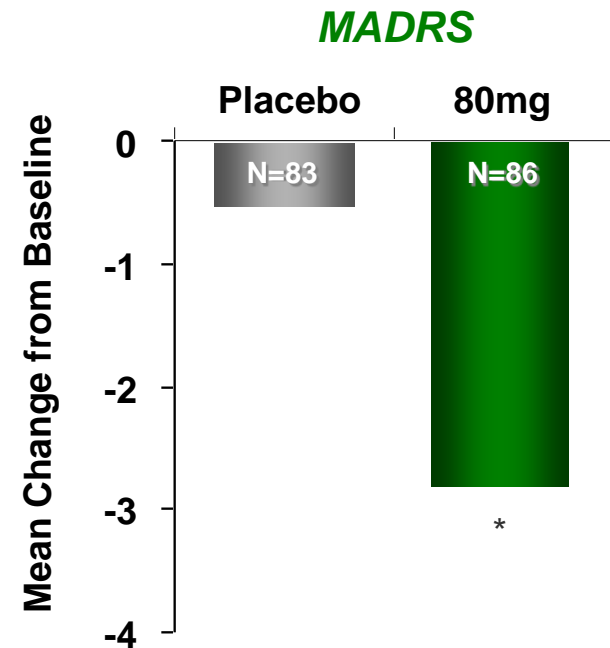
- Pharmacological profile
- Clinical data in schizophrenia and bipolar depression

Schizophrenia Program: Depressive Symptom Change - Pooled Data^a



**Baseline: Anxiety – Placebo 3.67, Lurasidone 3.83,
Depression – Placebo 2.90, Lurasidone 3.04**

LOCF at end point
**p*<0.05 using ANCOVA
^a*Studies 006, 196 – ECNP 2005*



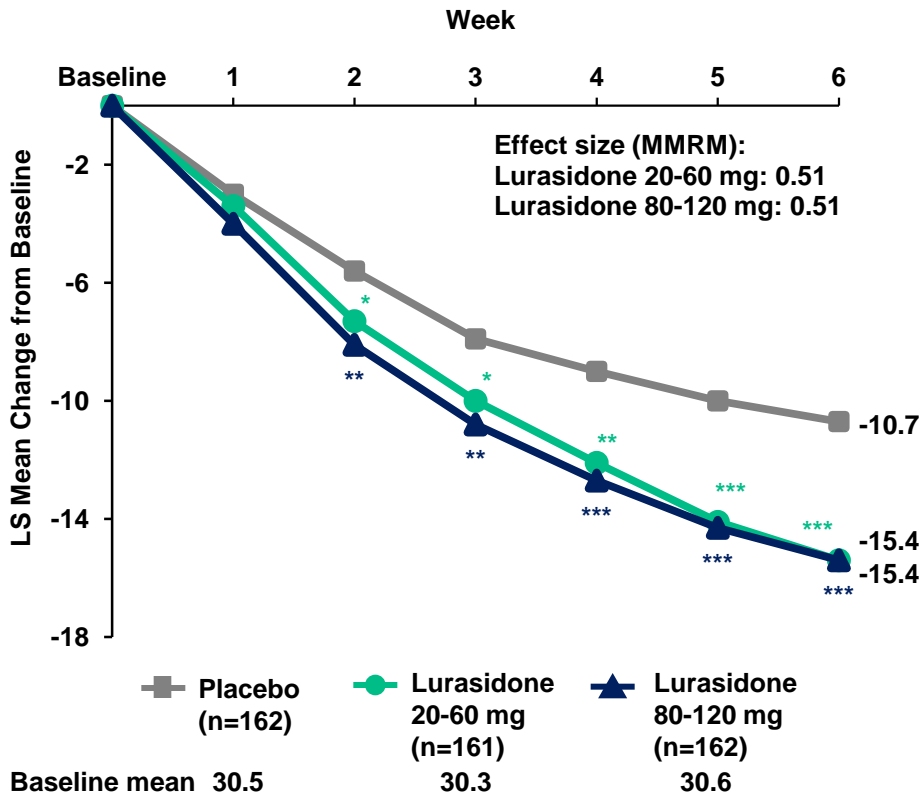
Baseline: Placebo 14.5, Lurasidone 14.2

LOCF at end point
**p*<0.05 using ANCOVA
^a*Study 196 – ECNP 2005*

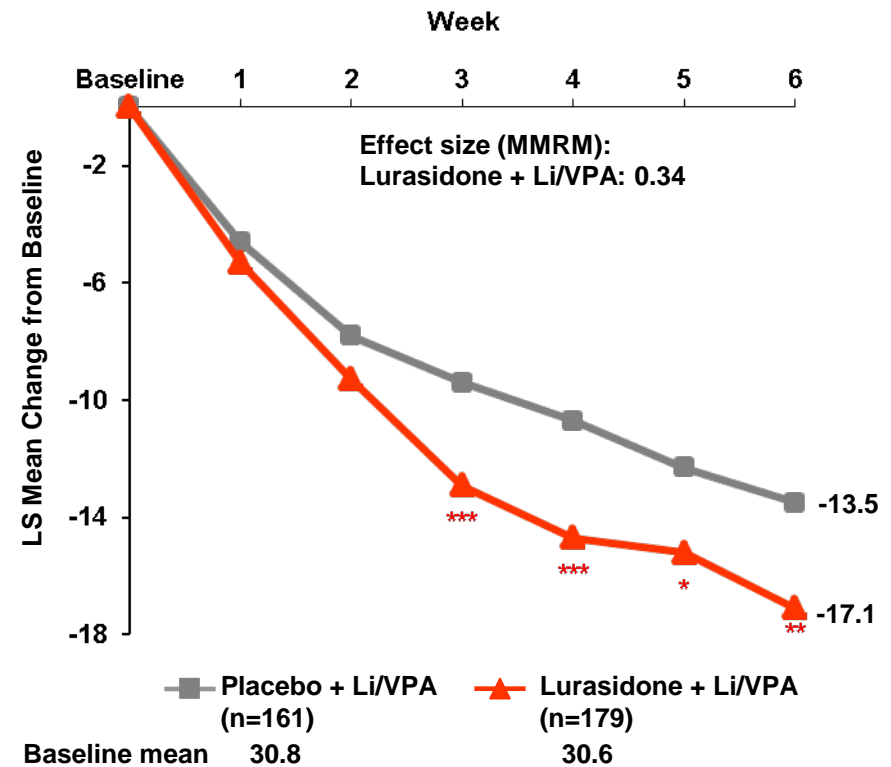
PREVAIL Studies in Bipolar Depression

MADRS: Primary Endpoint

PREVAIL Monotherapy



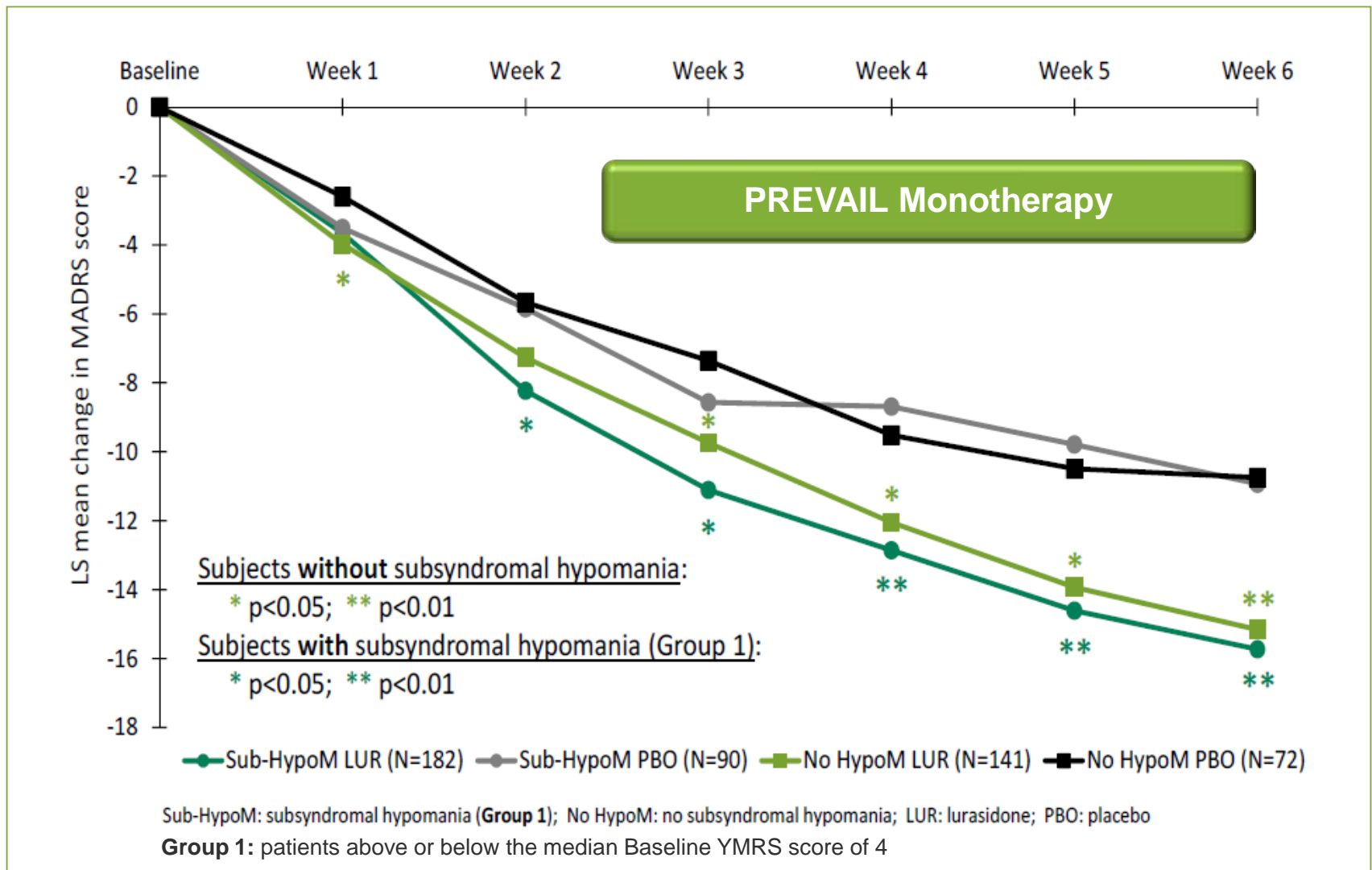
PREVAIL Adjunctive Therapy



* $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$.

Loebel A, et al., Am J Psych, in press 2013..

Post hoc analysis: MADRS Change for Subjects With and Without Subthreshold Hypomania



RESOLVE Study: Operational Criteria for Mixed Depression Diagnosis

- Full criteria for a Major Depressive Episode (at least 2 weeks in duration)

AND

- 2-3 manic symptoms occurring nearly every day (present for at least the past 2 weeks)
- Manic symptoms to be consistent with DSM 5 list (non-specific symptoms of irritability, distractibility and psychomotor agitation are excluded)

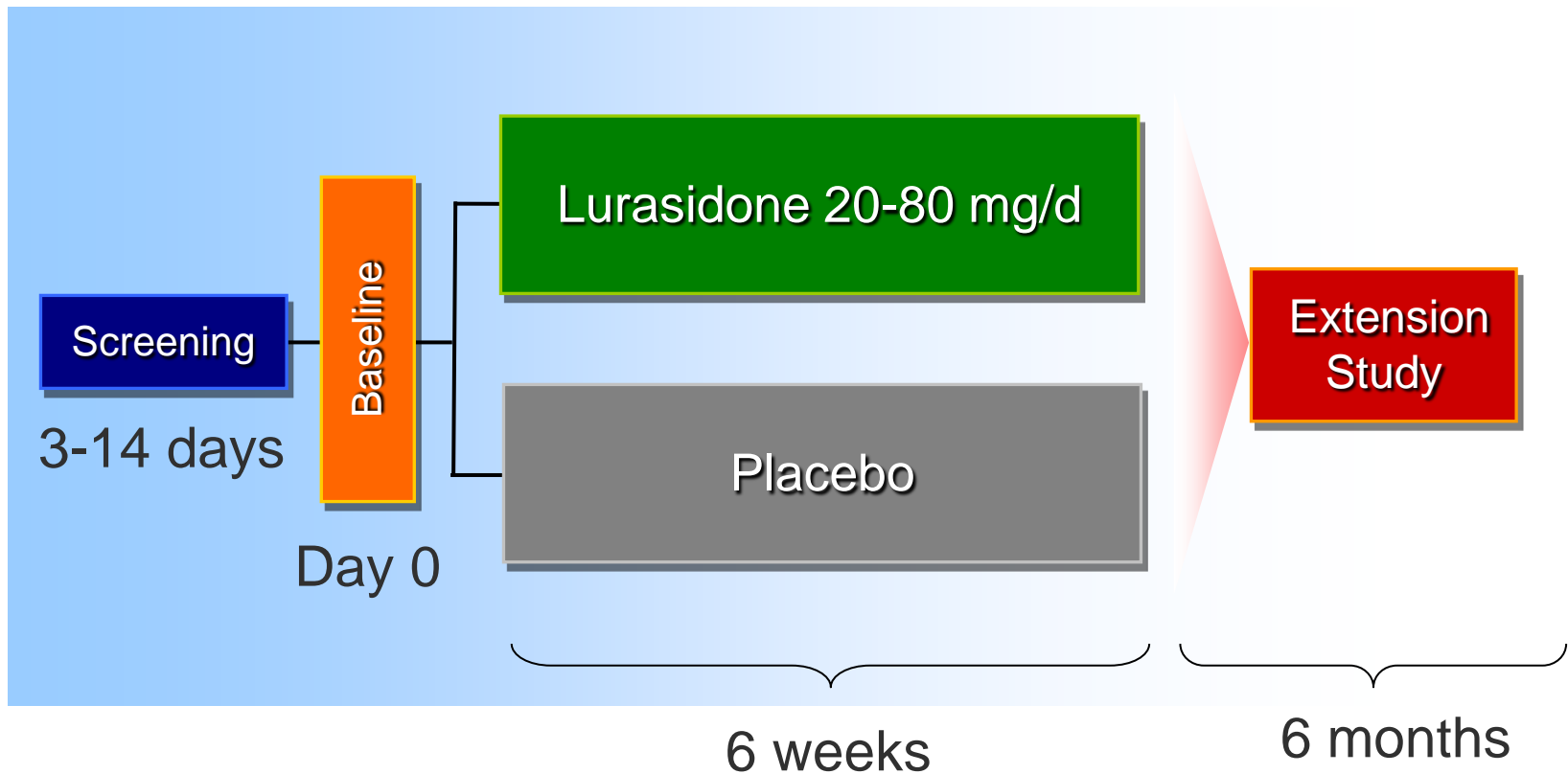
Convincing management to fund a novel program

- Opinion of academic experts and the relevant literature on high unmet medical need for this population
- Stressed rationale for use of lurasidone as a potential treatment
- Advocated for the position that this study, while being high risk, would contribute to a better understanding of this population
- Study could provide insights for future product development programs

RESOLVE Study Design

Double Blind

Open Label



Key Entry Criteria

- 18 to 75 years of age
- Diagnosed with an MDE (diagnosed by DSM-IV-TR, and confirmed by the modified SCID-CT)
- MADRS total score of ≥ 26 at both screening and baseline visits
- 2-3 manic symptoms to be consistent with DSM 5 list (non-specific symptoms of irritability, distractibility and psychomotor agitation are excluded)

**DO INVESTIGATORS UNDERSTAND
THE POPULATION UNDER STUDY?**

Ensuring accurate diagnosis

- Thorough discussion of the diagnosis at Investigator's Meetings
- Measures to validate and confirm the diagnosis included in trial procedures
- Modified SCID-CT (to include assessment of mixed features)

Objections to the Diagnosis

- The proposed diagnosis does not exist or is very rare
- Patients with this clinical presentation are bipolar spectrum patients
- Recruitment will be very difficult

I understand the criteria for diagnosis of a major depressive episode with mixed features (subthreshold hypomanic symptoms)

3%

1) I have no understanding of this diagnosis

5%

2) I have limited understanding of this diagnosis

35%

3) I have a moderate to good understanding of this diagnosis

57%

4) I fully understand this diagnosis

How often do you see patients with an episode of major depressive disorder with mixed features (subthreshold hypomanic symptoms) in clinical practice?

- 11%** 1) I rarely observe this condition (~2-3 cases/year)
- 48%** 2) I sometimes observe this condition (~1 case/month)
- 39%** 3) I often observe this condition (~1 case/week)
- 1%** 4) I never observe this condition

RESOLVE Study: Baseline Demographics

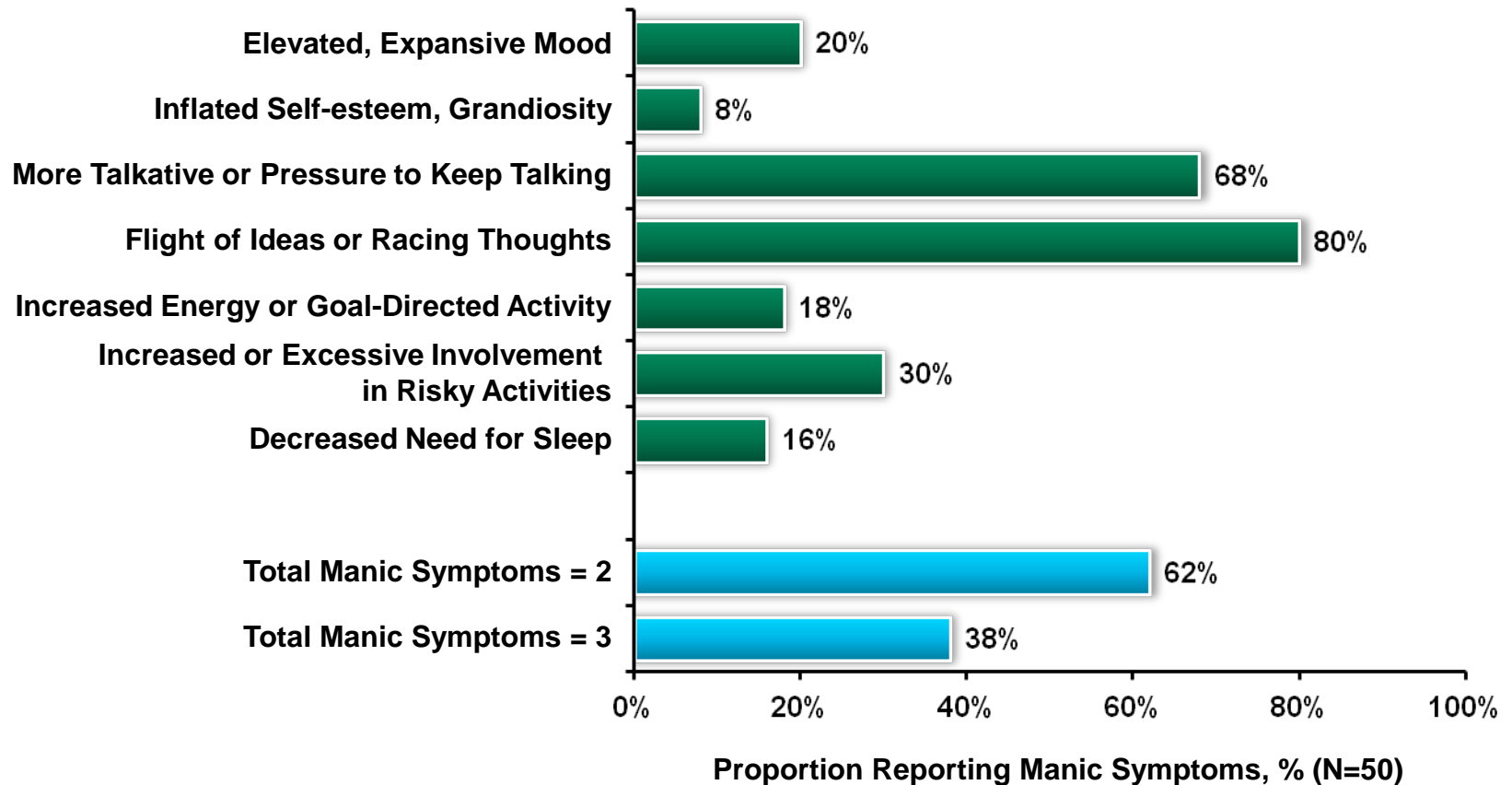
	Randomized Subjects (N=50)
Male, n (%)	14 (28.0%)
Age, years	
Mean (SD)	42.4 (14.7%)
Age ≤30, n (%)	12 (24.0%)
Age 31-50, n (%)	23 (46.0%)
Age ≥51, n (%)	15 (30.0%)
Race, n (%)	
Caucasian	29 (58.0%)
Black	19 (38.0%)
Other	2 (4.0%)

RESOLVE Study:

Baseline Clinical Characteristics

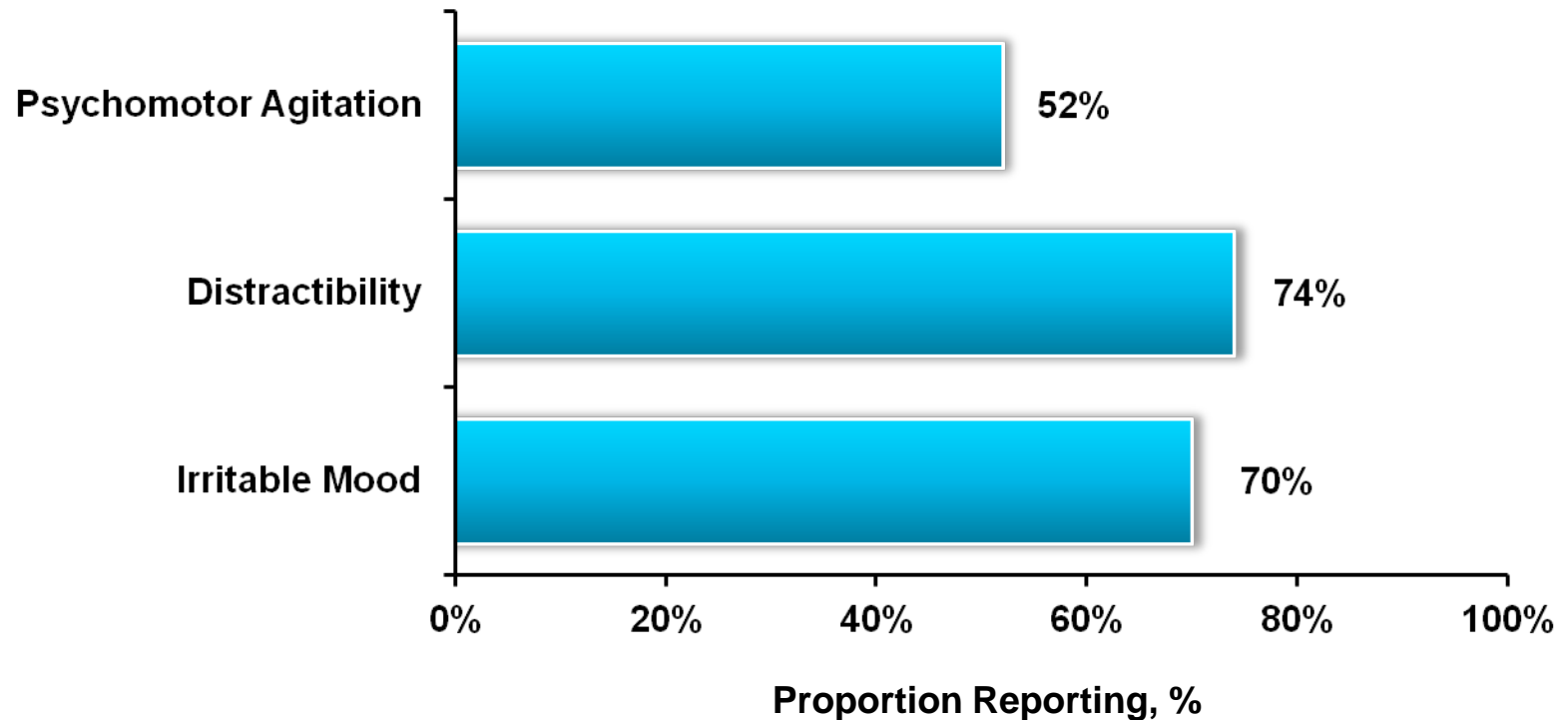
	Mean (SD)
Number of Lifetime Major Depressive Episodes	
Total Number	6.1 (6.4)
Number with Mixed Features	4.6 (5.9)
Duration of Current Episode, months	
Major Depressive Features	4.6 (3.2)
Concurrent Mixed Features	3.7 (3.3)
MADRS Score	33.2 (4.8)
CGI-S Score	4.6 (0.7)
YMRS Score	12.7 (5.0)
HAM-A Total Score	16.6 (6.9)
Sheehan Disability Scale Total Score	19.1 (6.3)

RESOLVE Study: Baseline Manic Symptoms



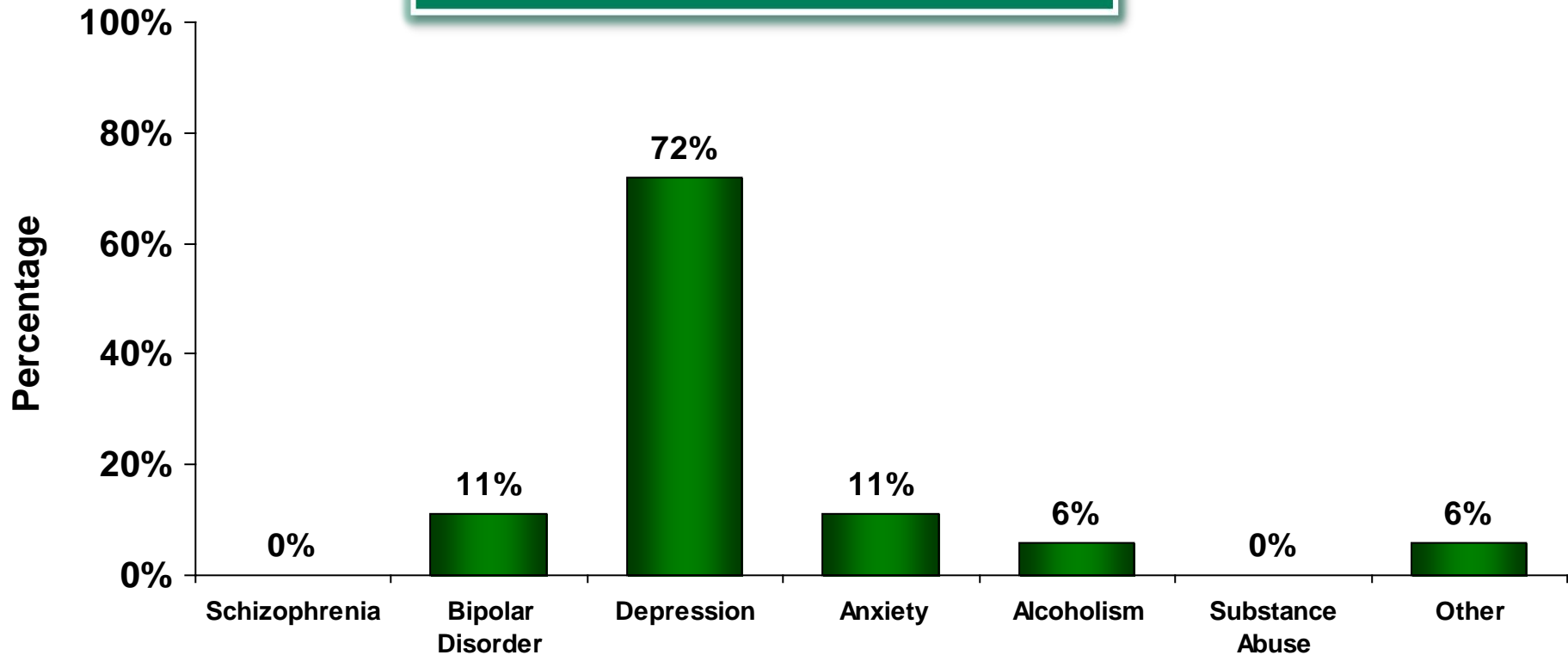
RESOLVE Study: Excluded Manic Symptoms

Frequency of manic symptoms occurring on most days in the past 2 weeks that are not included in the study or DSM-5 criteria for mixed depression

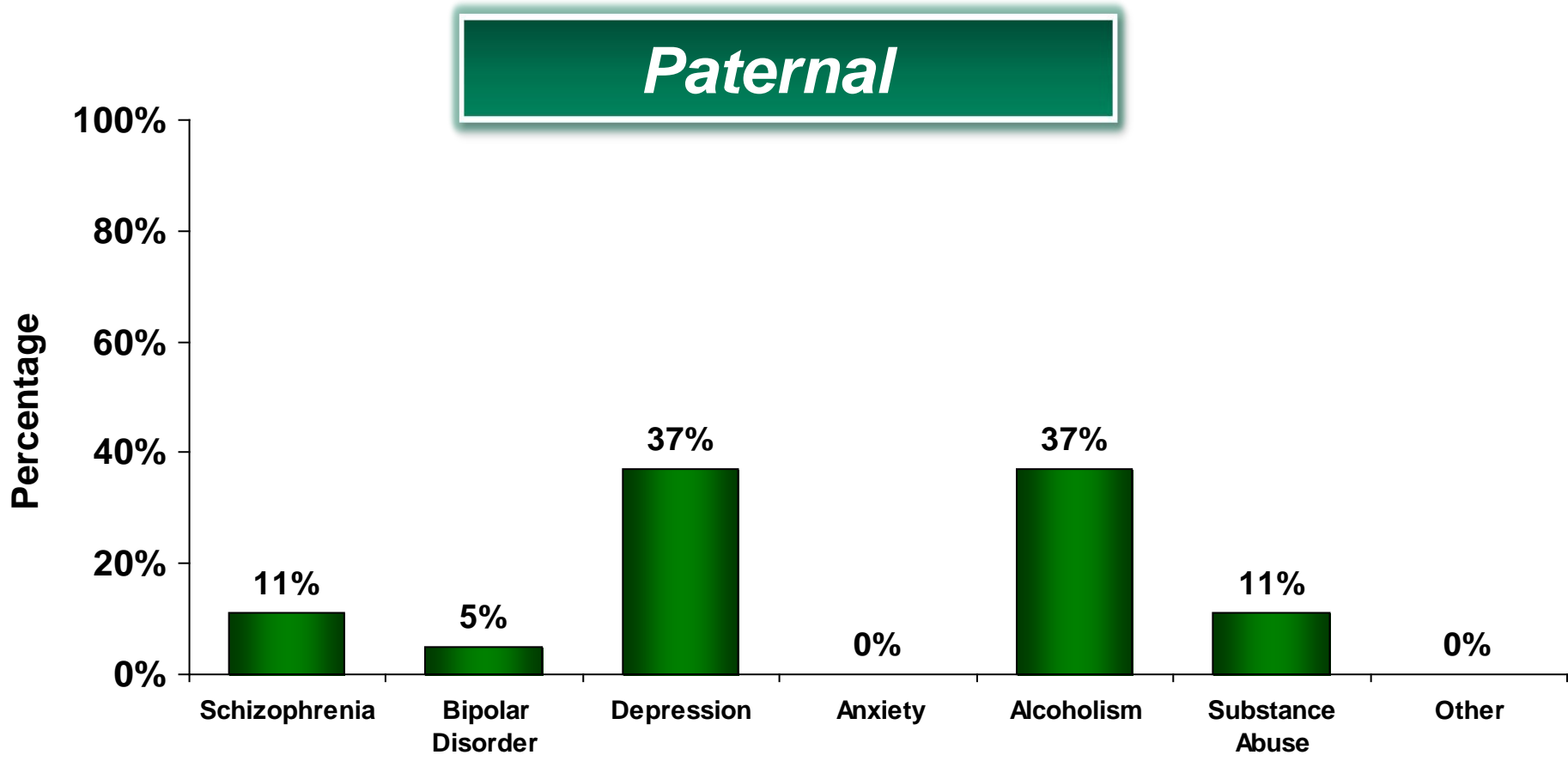


RESOLVE Study: Psychiatric Family History

Maternal



RESOLVE Study: Psychiatric Family History



Conclusions

- Innovative drug development within established drug classes can be pursued
- Requires thorough understanding of the pharmacologic and clinical profile of the molecule
- Education and discussion with investigators and other key stakeholders is needed