Supernus Pharmaceuticals

Pipeline Overview

November 2017

Safe Harbor Statement

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Robust Portfolio of CNS Products

Product	Indication	Development	NDA	Launch
Oxtellar XR®	Epilepsy			February 2013
Trokendi XR®	Epilepsy			August 2013
Trokendi XR®	Migraine			April 2017
SPN-810	Impulsive Aggression	Phase III		
SPN-812	ADHD	Phase III		
Oxtellar XR®	Bipolar	Phase I/II		
SPN-809	Depression	IND/Phase II Ready		

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SPN-810 Impulsive Aggression

Daniel Connor, M.D.
Lockean Distinguished Professor of Psychiatry
Chief, Division of Child and Adolescent Psychiatry
University of Connecticut School of Medicine

From Investor Day – June 2015

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Aggression

- **Definition:** A forceful action or procedure resulting in an unprovoked attack on another or engaging in hostile, destructive, or injurious behavior. *Webster's Ninth New Collegiate Dictionary* (1989).
- Aggression as a concept is distinct from antisocial behavior, delinquency, conduct problems, disruptive behavior disorders, irritability, Oppositional Defiant Disorder, or Conduct Disorder.

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Aggression Can Be Divided into Two Groups

Adaptive Aggression

- "Appropriate"
- Serves identifiable goals
- Brain structure and / or function not impaired
- Does not require mental health research or treatment

Maladaptive Aggression

- "Excessive" or "Inappropriate"
- Does not serve identifiable goals
- Brain structure and / or function impaired
- May require psychiatric and pharmacological treatment

Connor, 2002; Wakefield, 1992

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Maladaptive Aggression Has Societal Impacts

- Occurs in 40% to 60% of all patients **referred** to child psychiatrists
- Predicts **rehospitalization** rates regardless of diagnosis in youths discharged from inpatient settings
- Associated with **staff injury** in residential care
- Associated with **polypharmacy** (multiple medications) in inpatient children and adolescents regardless of diagnosis or comorbidity
- Early onset (before age 10) predicts **poor lifetime prognosis**
- **Annual costs to society** are up to six times the rate for non-conduct disorder youths

Connor, 2002; Steiner & Karnik, 2003; Blader, 2004; Cunningham et al, 2003; Edelsohn et al, 2003; Connor et al. 1997; Moffitt, 1993; Scott et al, BMJ 2001; Waters et al, Health Policy, 2005

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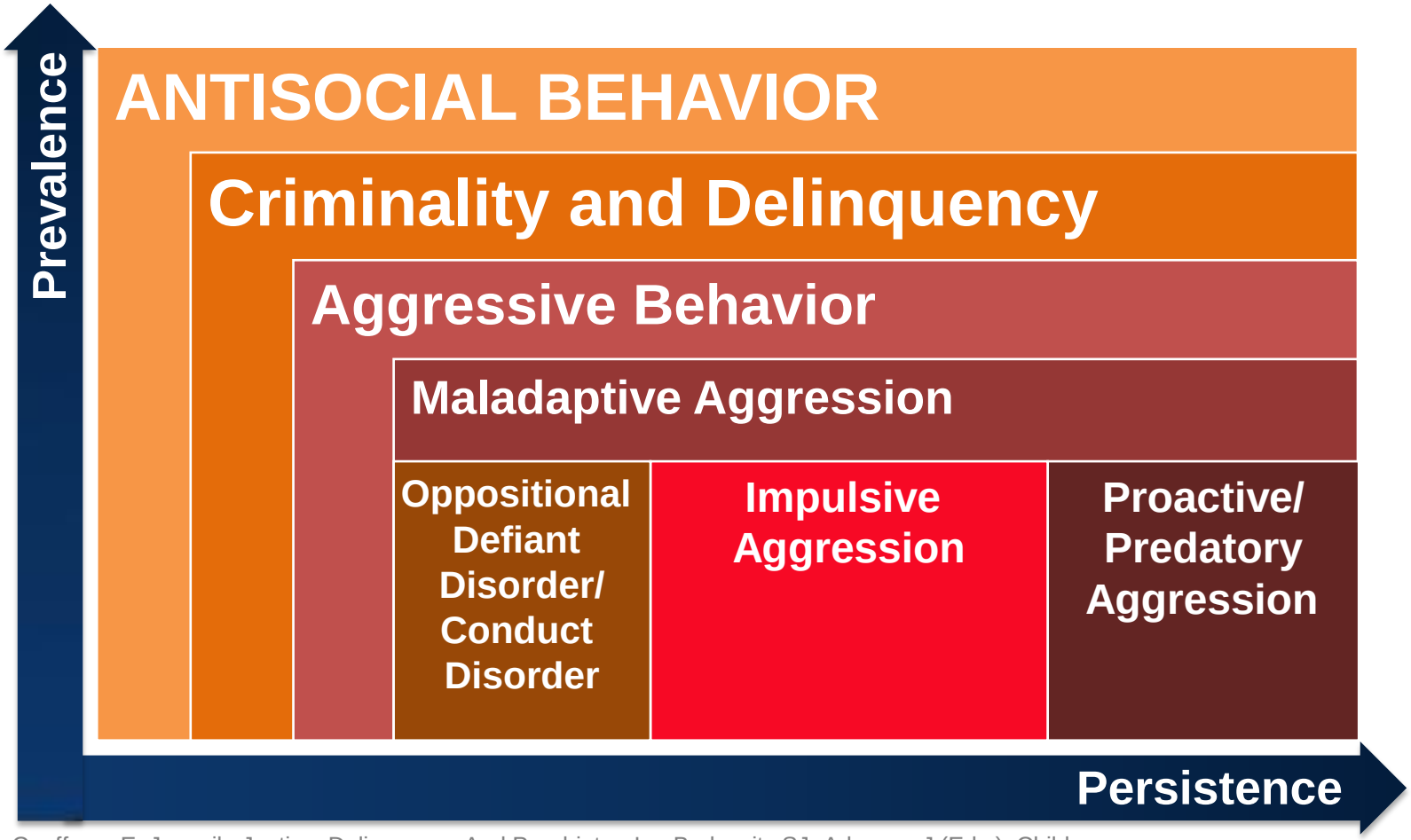
Impulsive Aggression is Part of a Landscape of Maladaptive Aggressive Behaviors



Steiner, H. Cauffman E. Juvenile Justice, Delinquency And Psychiatry. In: Berkowitz SJ, Adnopoz J (Eds.): Child And Adolescent Psychiatric Clinics Of North America, 7(3): 653-672, The Child Psychiatrist In The Community. Philadelphia, W.B. Saunders,1998.

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Understanding Impulsive Aggression

- Impulsive Aggression is a subtype of Maladaptive Aggression
- Impulsivity can be defined neurobiologically
  - Short fuse that causes impairment in the context of neuropsychiatric illness
  - Lack of self-control results in harm to patient with impulse control issues
- Analogous to fever as a symptom of underlying medical / surgical disease

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Impulsive Aggression Occurs Across Multiple Disorders

- ADHD
- Autism Spectrum Disorder
- Bipolar Disorder
- Oppositional Defiant Disorder
- Conduct Disorder
- Intermittent Explosive Disorder
- Disruptive Mood Dysregulation Disorder
- Schizophrenia
- Alzheimer's Disease
- PTSD and Disorders of Traumatic Stress
- Substance Use Disorder
- Anxiety Disorders
- Psychosis
- Somatic neurological impairments
  - Traumatic Brain Injury
  - Encephalitis
  - Stroke
  - Epilepsy

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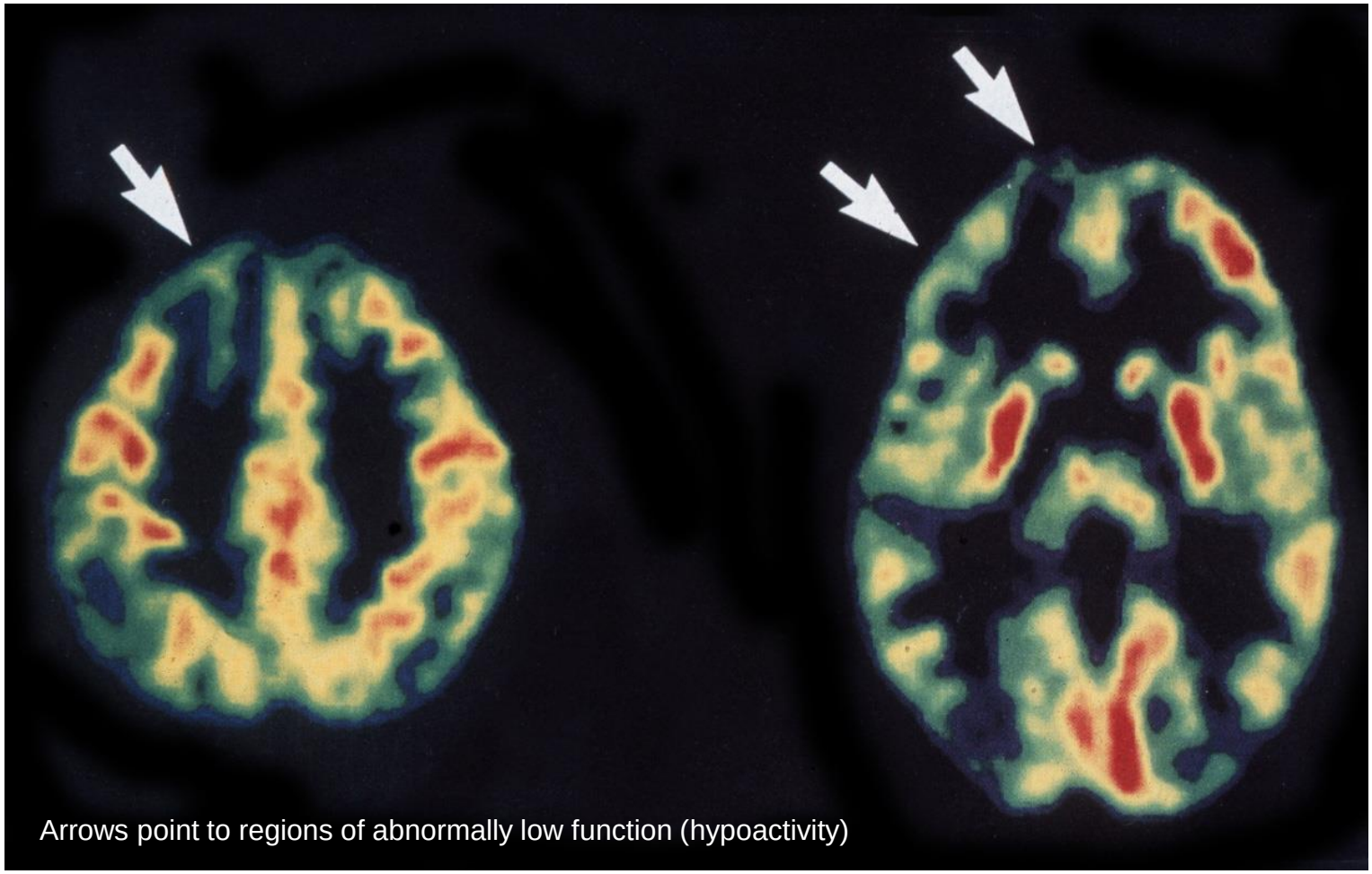
ADHD is the Most Common Neurobehavioral Disorder in Children



SPECT image of 5 year old ADHD patient

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Prevalence of Impulsive Aggression

- Survey shows Impulsive Aggression in 22.5%–32% of children with ADHD
  - 1092 patient chart review
  - 120 child and adolescent psychiatrists, 32 child neurologists, and 30 developmental and behavioral pediatricians
  - Nationwide sample
- ADHD prevalence ≈ 5–7% of children worldwide

Market sizing and demand study, April 2015; Thomas R et al, Pediatrics. 2015 Apr;135(4) Epub 2015 Mar 2.

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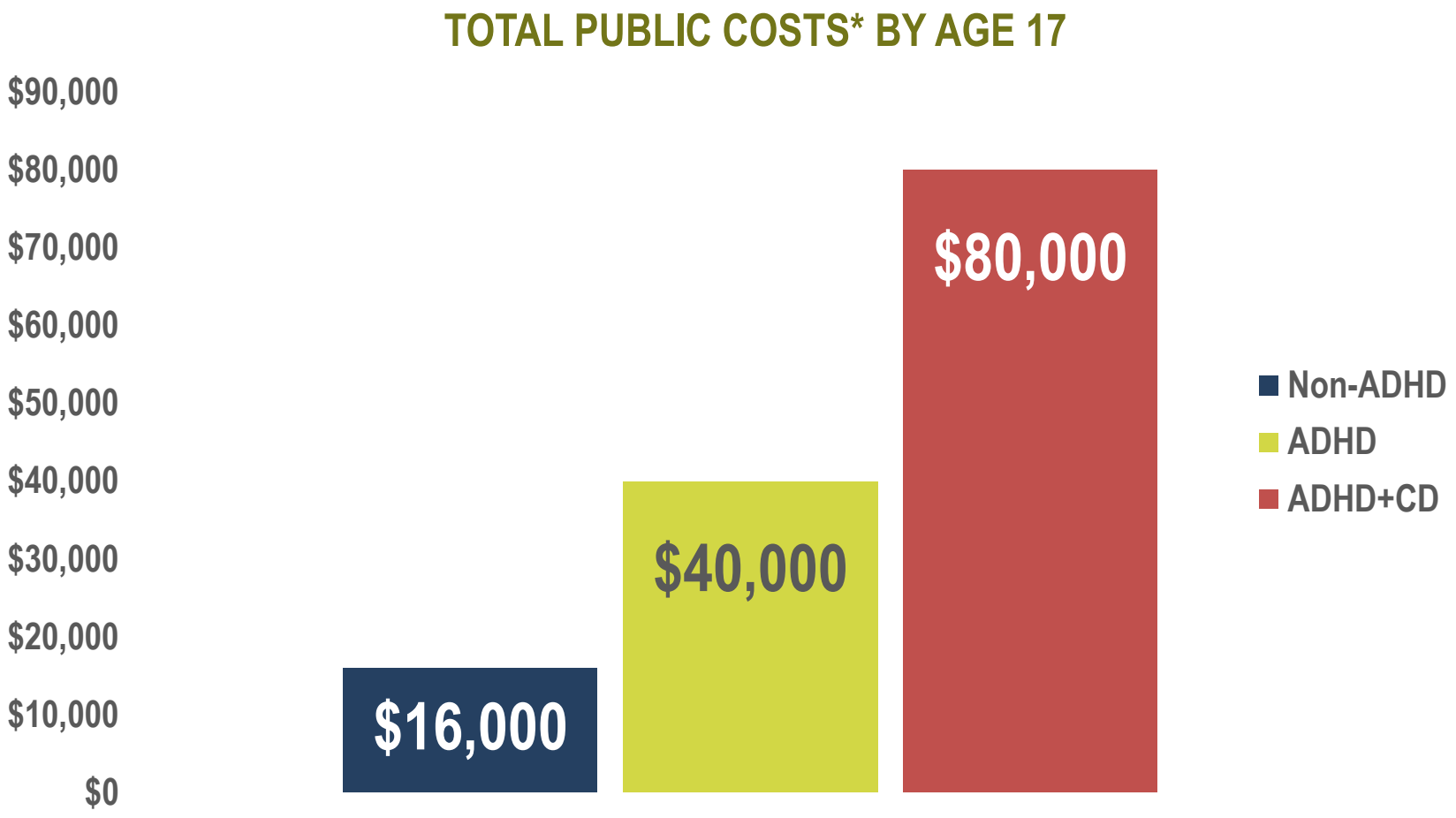
ADHD and Conduct Disorder Result in Higher Public Healthcare Costs



*Health care + mental health care + juvenile justice + school costs

Conduct Problems Prevention Group (2009): The Journal of Behavioral Health Services & Research 36(4): 436-449.

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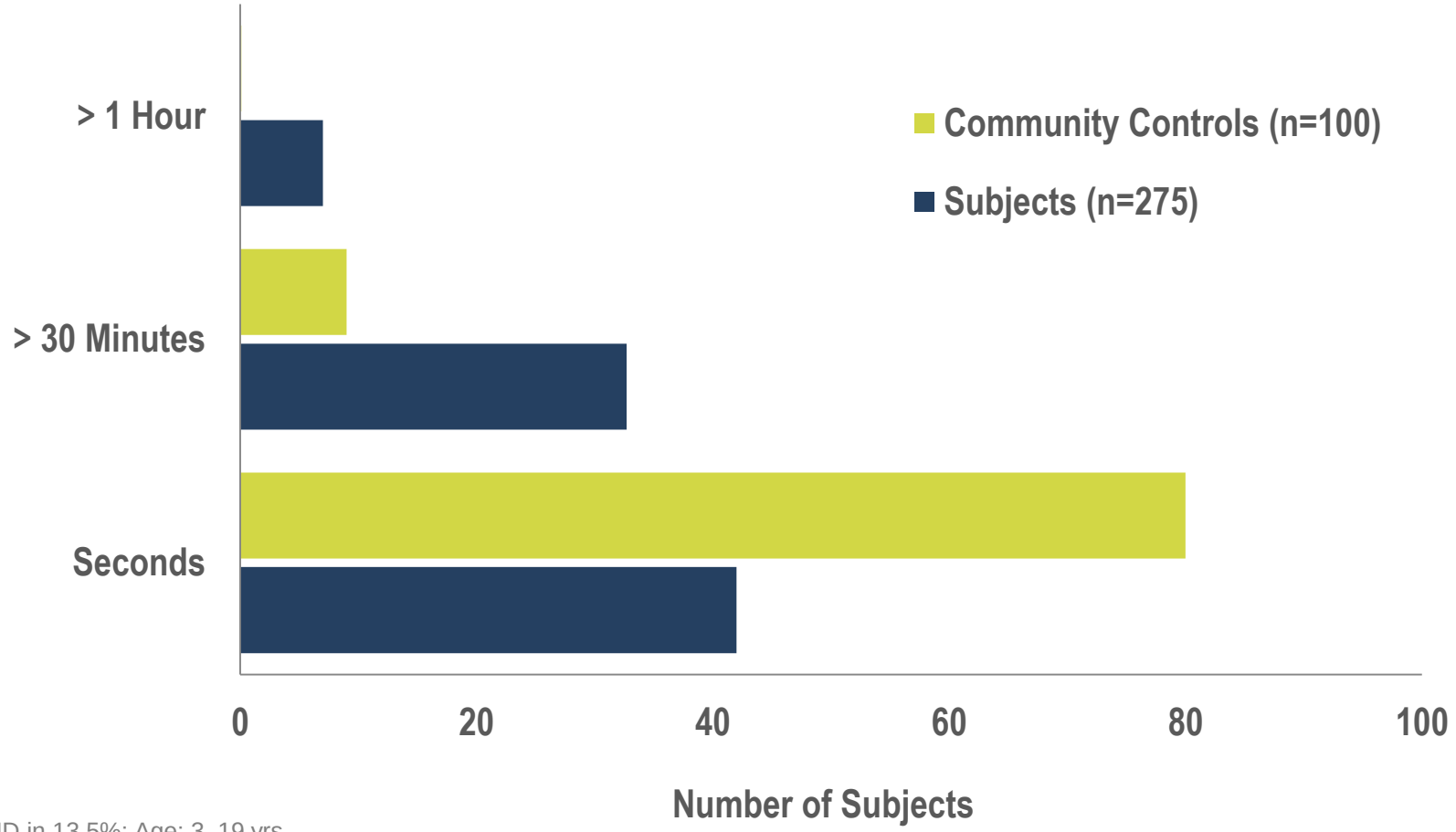
Impulsive Aggression Episodes in Children / Adolescents Last Longer



ADHD in 13.5%; Age: 3–19 yrs

Bambauer & Connor, CNS Spectr. 2005,10(9):709.

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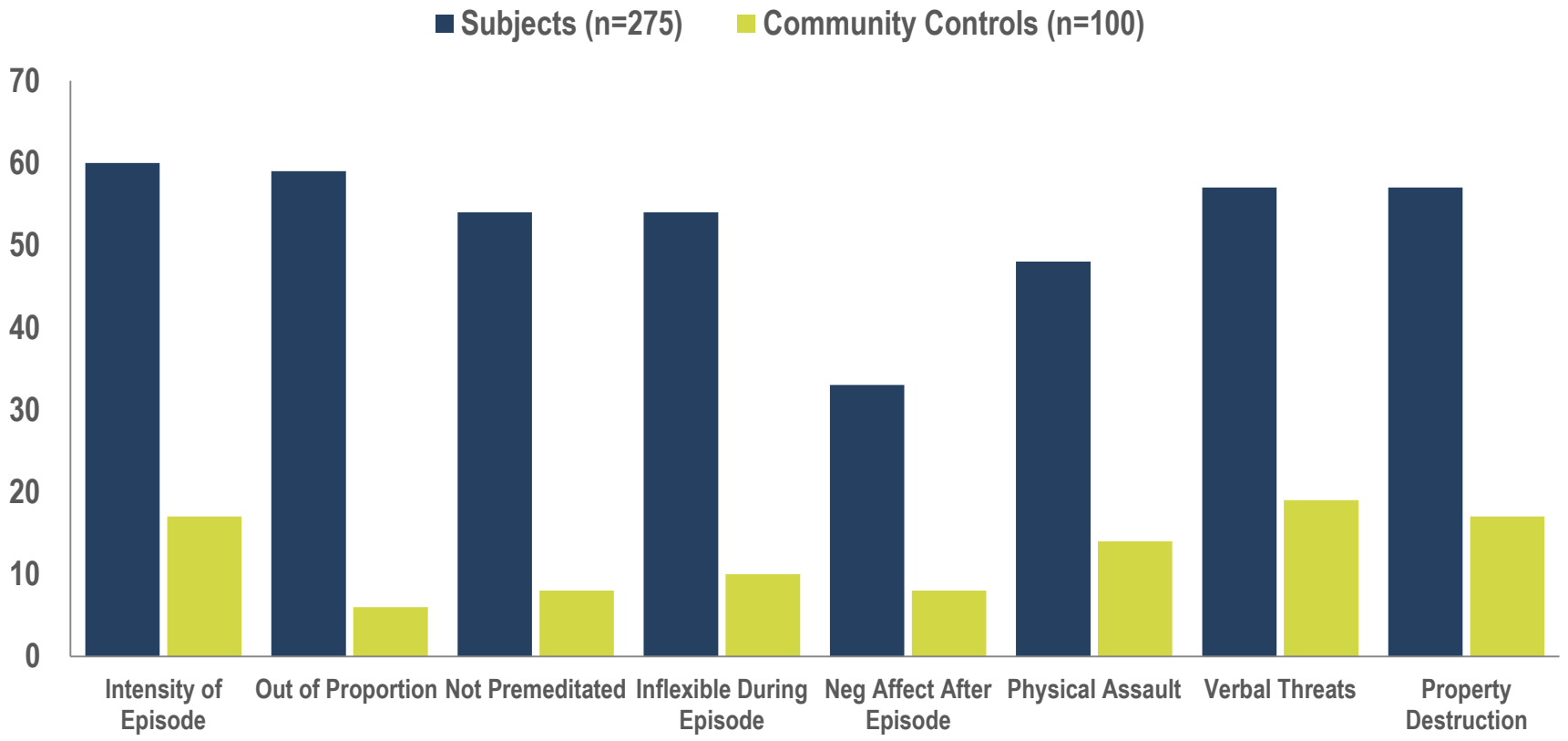
Characteristics of Impulsive Aggression in Children / Adolescents



ADHD in 13.5%; Age: 3–19 yrs

Bambauer & Connor, CNS Spectr. 2005,10(9):709.

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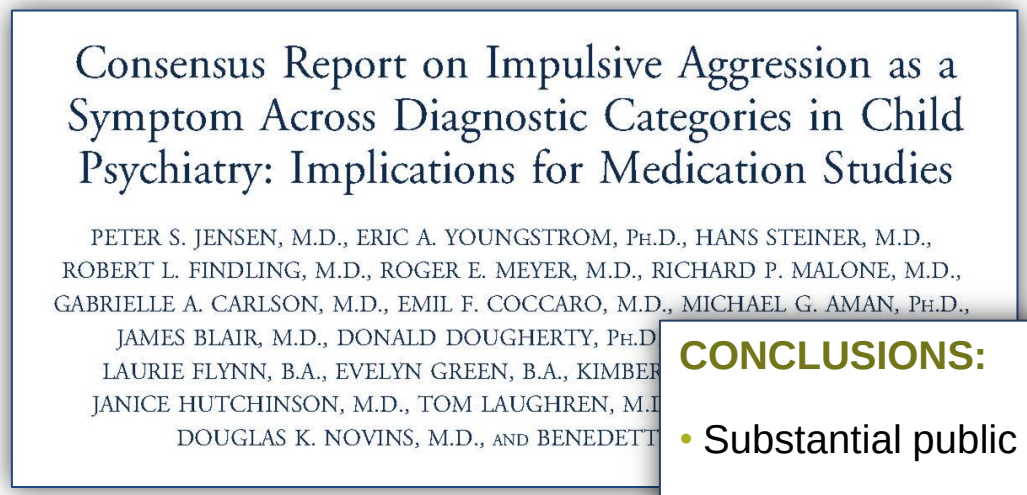
2007 Landmark Paper Defines Substantial Clinical and Public Health Concerns in Impulsive Aggression



Consensus Report on Impulsive Aggression as a Symptom Across Diagnostic Categories in Child Psychiatry: Implications for Medication Studies

PETER S. JENSEN, M.D., ERIC A. YOUNGSTROM, PH.D., HANS STEINER, M.D., ROBERT L. FINDLING, M.D., ROGER E. MEYER, M.D., RICHARD P. MALONE, M.D., GABRIELLE A. CARLSON, M.D., EMIL F. COCCARO, M.D., MICHAEL G. AMAN, PH.D., JAMES BLAIR, M.D., DONALD DOUGHERTY, PH.D LAURIE FLYNN, B.A., EVELYN GREEN, B.A., KIMBER JANICE HUTCHINSON, M.D., TOM LAUGHREN, M.I DOUGLAS K. NOVINS, M.D., AND BENEDETT

CONCLUSIONS:

- Substantial public health concern
- Substantial clinical concern
- Identifiable and constitutes a key therapeutic target across multiple disorders
- Can be measured with sufficient precision that pharmacological studies are warranted
- Should be studied within well-defined clinical disorders such as ADHD, autism, bipolar disorder

JAACAP, 2007:46(3):309-322.

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Existing Tools Do Not Specifically Measure Impulsive Aggression

- Some touch on, but don't specifically measure Impulsive Aggression
- Some rate overt aggression
- Others touch on relevant aspects of physiology
- Response criteria for the treatment of Impulsive Aggression need to be standardized

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Impulsive Aggression is A Significant Health Concern Requiring Pharmacological Intervention

- Clear distinction between Impulsive Aggression and other forms of aggression
  - Occurs outside of expected social context or preceding event
  - Disproportionate to causes in frequency, intensity, duration, and / or severity
  - Prolonged and does not terminate readily
- Associated with substantial daily impairment in functioning with implications in public health
- Substantial need to develop specific tools and treatments for impulsive aggression

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SPN-810 Clinical Perspective

Robert Findling, M.D.
VP of Psychiatric Services & Research, Kennedy Krieger Institute
Director, Child and Adolescent Psychiatry, Johns Hopkins Medicine

From Investor Day – June 2015

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Stimulant Optimization is First Step in Managing Impulsive Aggression in ADHD

- No FDA approved treatments for Impulsive Aggression

Optimize ADHD Stimulant

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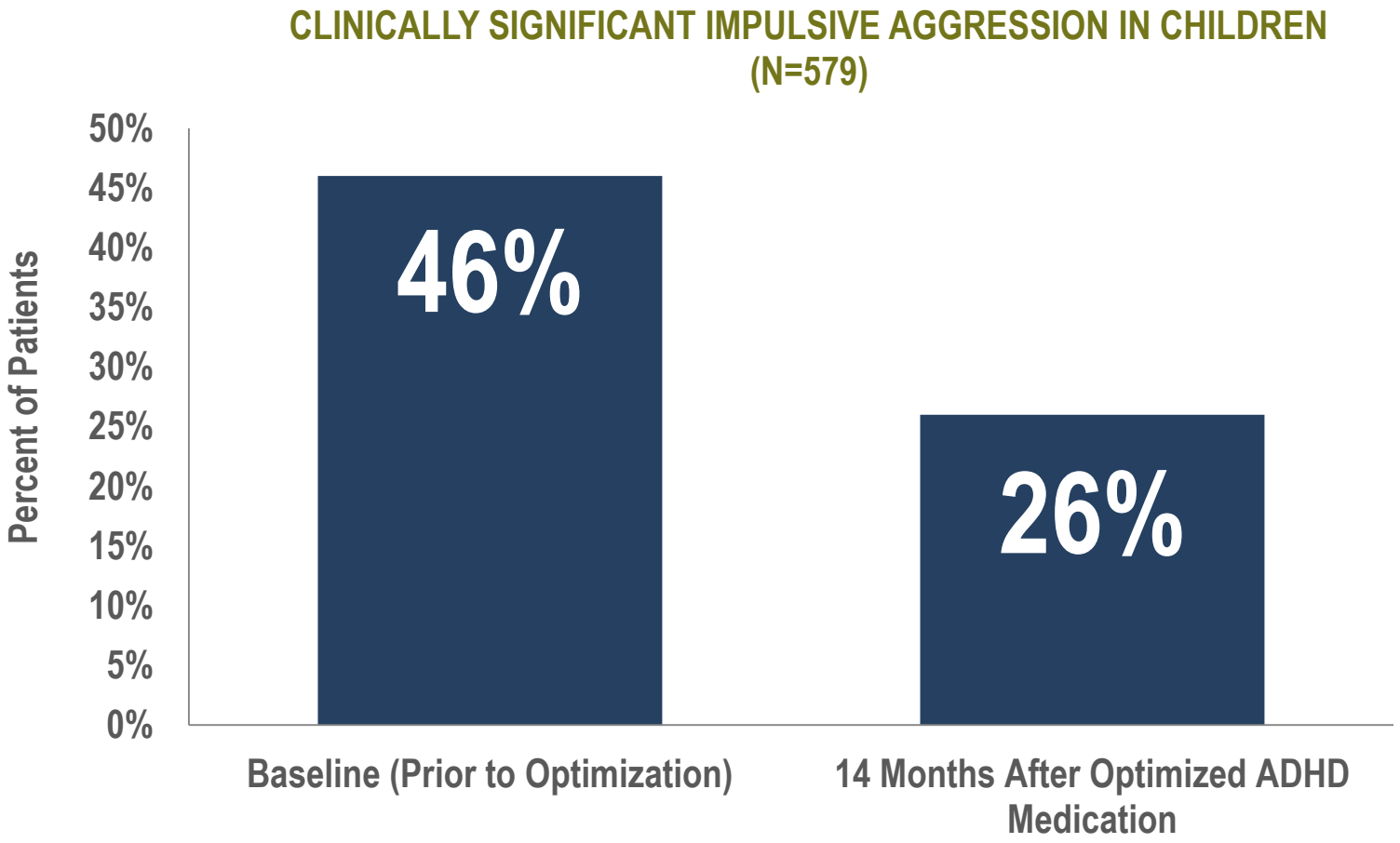
Impulsive Aggression Symptoms Still Present After Optimized ADHD Treatment



MTA Cooperative Group, Arch Gen Psychiatry, 1999; 56:1073–1086.; Jensen et al, JAACP, 46:3, March 2007

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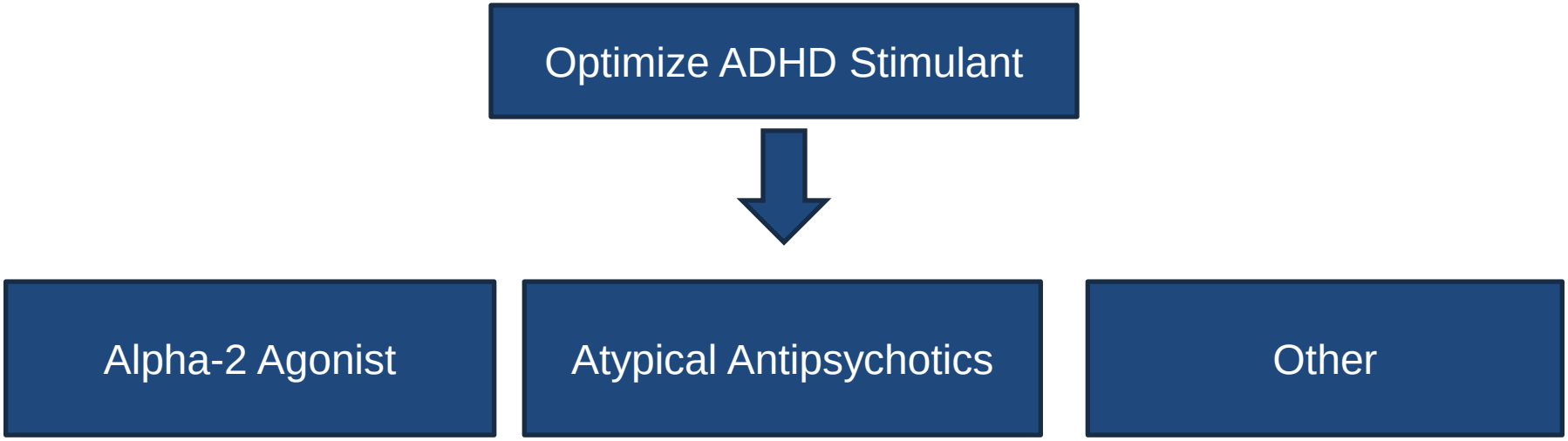
Following Stimulant Optimization, Off-Label Agents are Used for Remaining Aggression

- No FDA approved treatments for Impulsive Aggression



Existing Atypical Antipsychotics in Children with ADHD Have Limitations

Side Effect	Description	Abilify (aripiprazole)	Risperdal (risperidone)
Weight Gain		+	++
Type 2 Diabetes		+	+
Sedation		+	+
Dyslipidemia	Abnormal lipid level changes (LDL, HDL, Cholesterol, Triglycerides)	+	+
Extrapyramidal Symptoms	Drug induced movement disorders	+	++
Hyperprolactinemia	Elevated prolactin	0	+++
Postural Hypotension	Low blood pressure when standing from sitting	+	+
Prolonged QT Interval	Heart arrhythmia	+	+

0= rare; +=lower risk; ++= medium risk; +++=higher risk

Adapted from Meunch et al: Am Fam Physician 2010 Mar 1, 81 (5): 617–622

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Unmet Needs Exist for Treatments Specific for Impulsive Aggression

- No FDA approved treatments for Impulsive Aggression

Optimize ADHD Stimulant

Alpha-2 Agonist	Atypical Antipsychotics	Other
• Limited data in impulsive aggression • Relatively benign safety profile: mild to moderate somnolence, headache, sedation	• Effective for aggression • Significant side effects include elevated prolactin levels, increased weight gain, extrapyramidal symptoms, metabolic changes, sedation	• Limited data in aggressive population

CNS Drugs. 2010 Sep;24(9):755-68; Can J Psychiatry. 2015 Feb 1;60(2):52-61

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SPN-810: Promising Candidate for Impulsive Aggression Treatment

- Originally marketed by Endo Pharmaceuticals as Moban® for the treatment of schizophrenia in 1974[1]
  - Marketing discontinued for commercial reasons in 2010
- Moban® dosing as high as 225 mg / day
- SPN-810 to be dosed ≤ 36 mg / day

[1]Federal Register. https://www.federalregister.gov/articles/2013/11/06/2013-26550/determination-that-moban-molindone-hydrochloride-tablets-5-milligrams-10-milligrams-25-milligrams-50. Accessed November 3, 2014;

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SPN-810: Promising Candidate for Impulsive Aggression Treatment

- Extended Release Molindone Hydrochloride
  - Potent D2 antagonist (Efficacy)
  - Low H1 binding (Tolerability; e.g. weight gain)
  - Low 5-HT2C (Tolerability; e.g. weight gain)
- Anticipated to be first FDA approved product for Impulsive Aggression in children/adolescents with ADHD
- Potential differentiation includes less impact on:
  - Weight gain
  - Sedation rates
  - Prolactin levels
  - Extrapyramidal symptoms (EPS)

Neuropsychopharmacology (2003) 28, 519-526.

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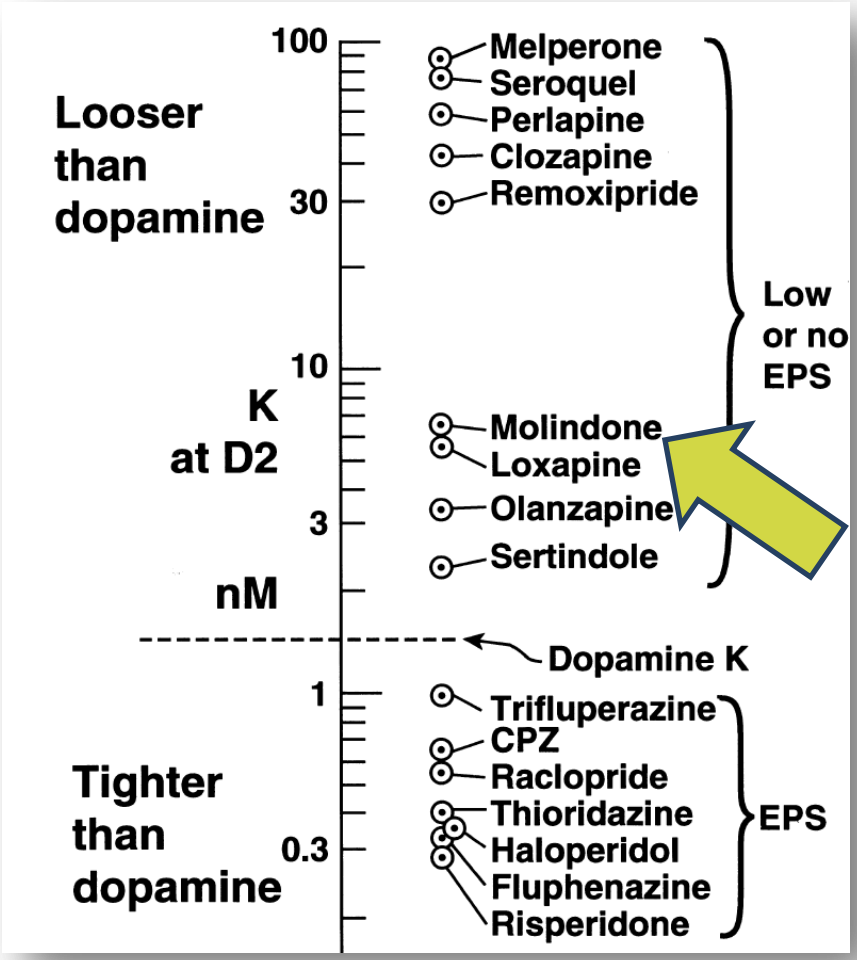
Potential for Lower Rates of EPS Due to Looser D2 Binding



- Molindone binds more loosely to the D2 receptor than risperidone
- Antipsychotics which bind more loosely than dopamine elicit little or no Parkinsonism or other extrapyramidal clinical signs in patients
  - Symptoms of tremor, bradykinesia (slowness in executing movement), rigidity, and postural instability

Seeman P, Tallerico T. Mol Psychiatry. 1998;3(2):123-134.

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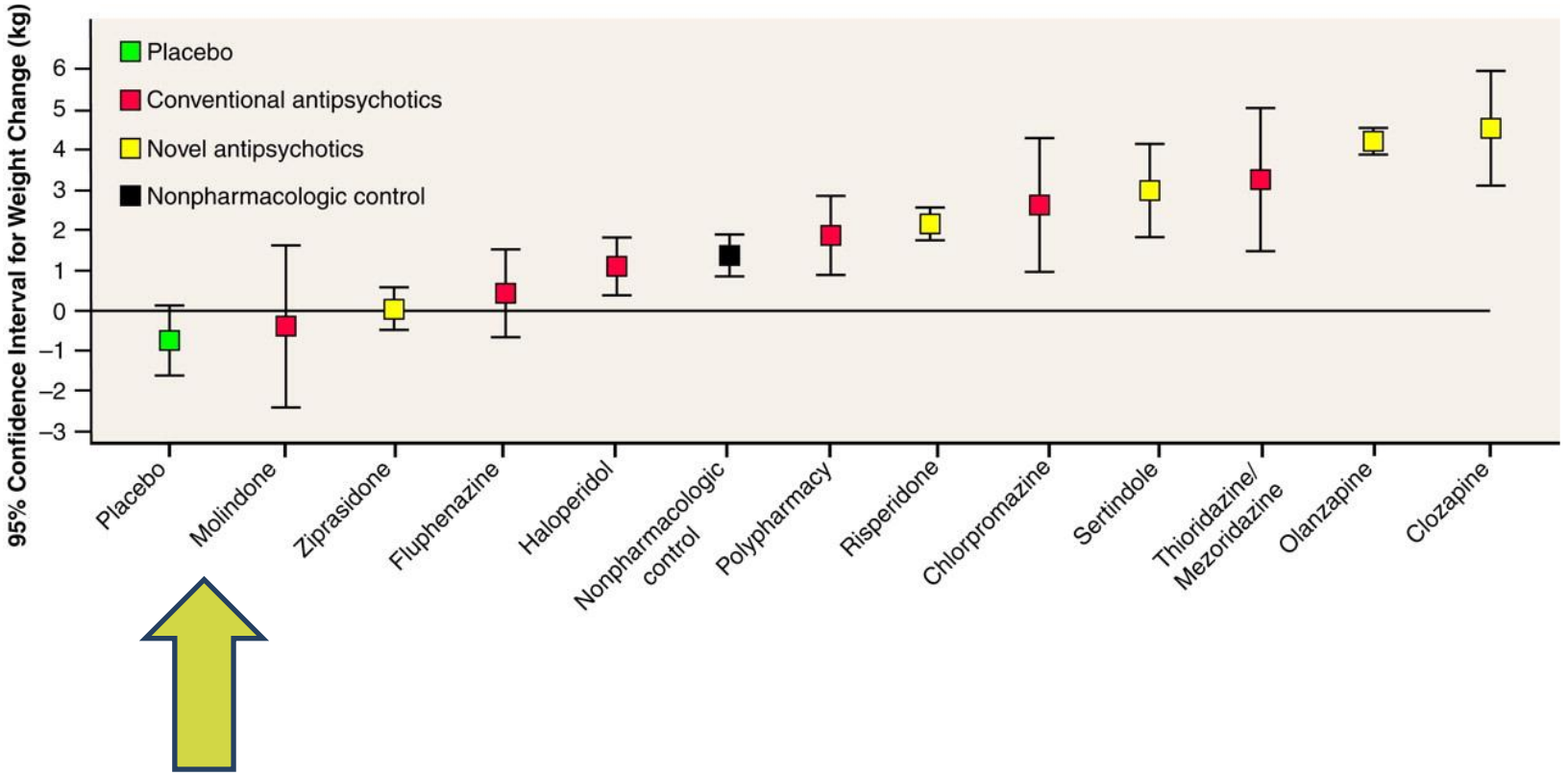
Molindone Exhibited Least Weight Gain Compared to Other Antipsychotics



Allison DB, et al. *Am J Psychiatry*. 1999;156(11):1686-1696.

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TEOSS Study Demonstrated Molindone Safety Profile in Pediatric Population

- Evaluated 119 children (early onset schizophrenia and schizoaffective disorder)

Product	Dose Range (mg/day)	Mean Dose (mg/day)
Olanzapine	2.5 – 20	11
Risperidone	0.5 – 6	3
Molindone	10 – 140	60

Am J Psychiatry. 2008 Nov;165(11):1420-31.

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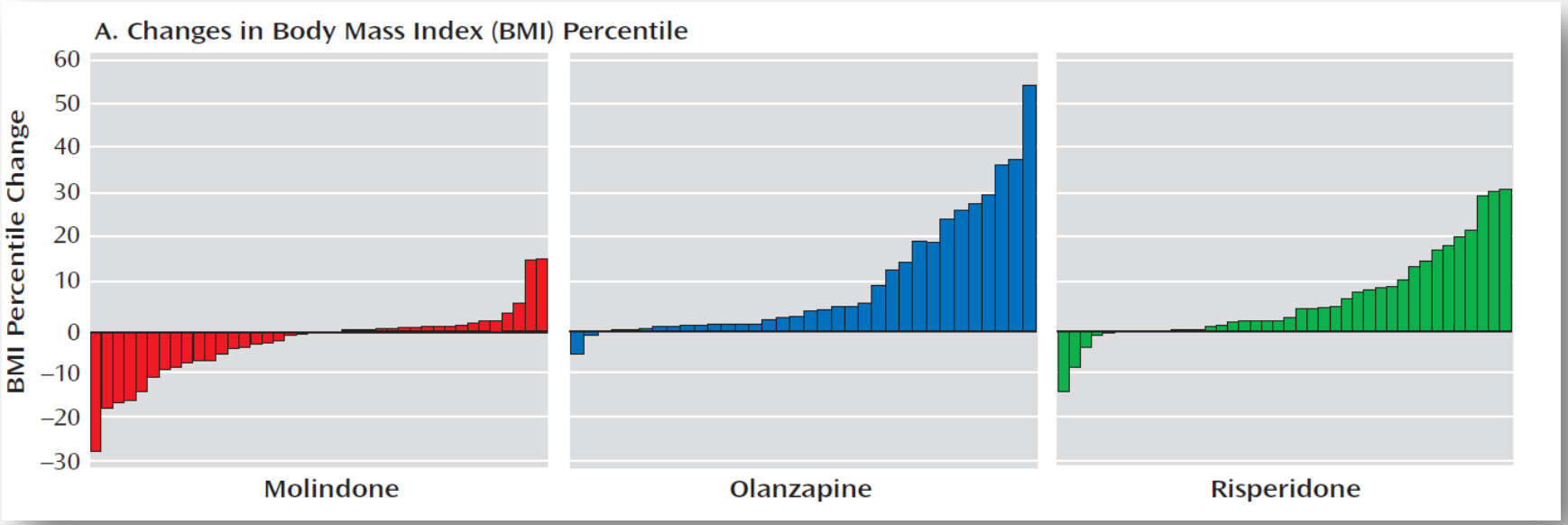
Molindone Exhibited Less Weight Gain



Am J Psychiatry. 2008 Nov;165(11):1420-31.

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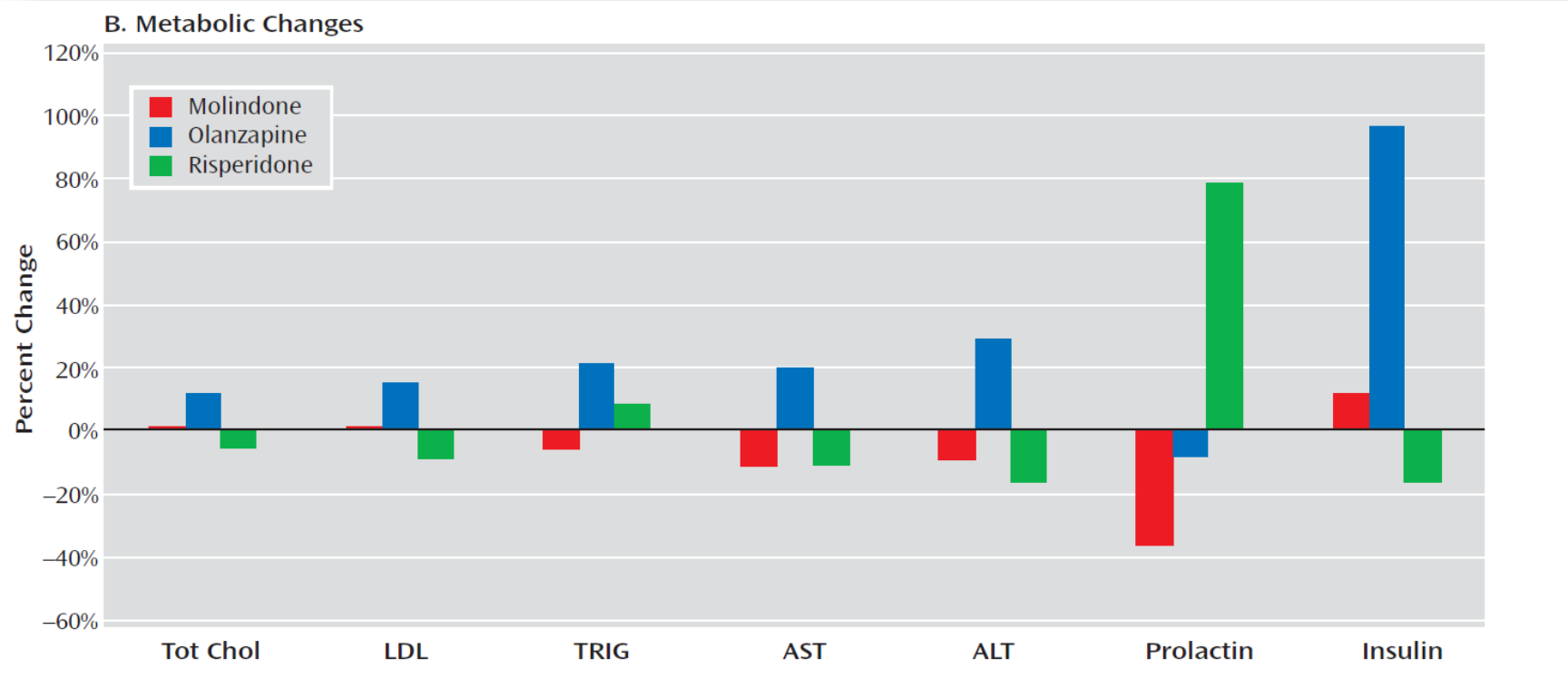
Molindone Showed Significantly Less Effect on Metabolism



Measures of Liver Function - AST: aspartate aminotransferase; ALT: alanine transaminase

Am J Psychiatry. 2008 Nov;165(11):1420-31.

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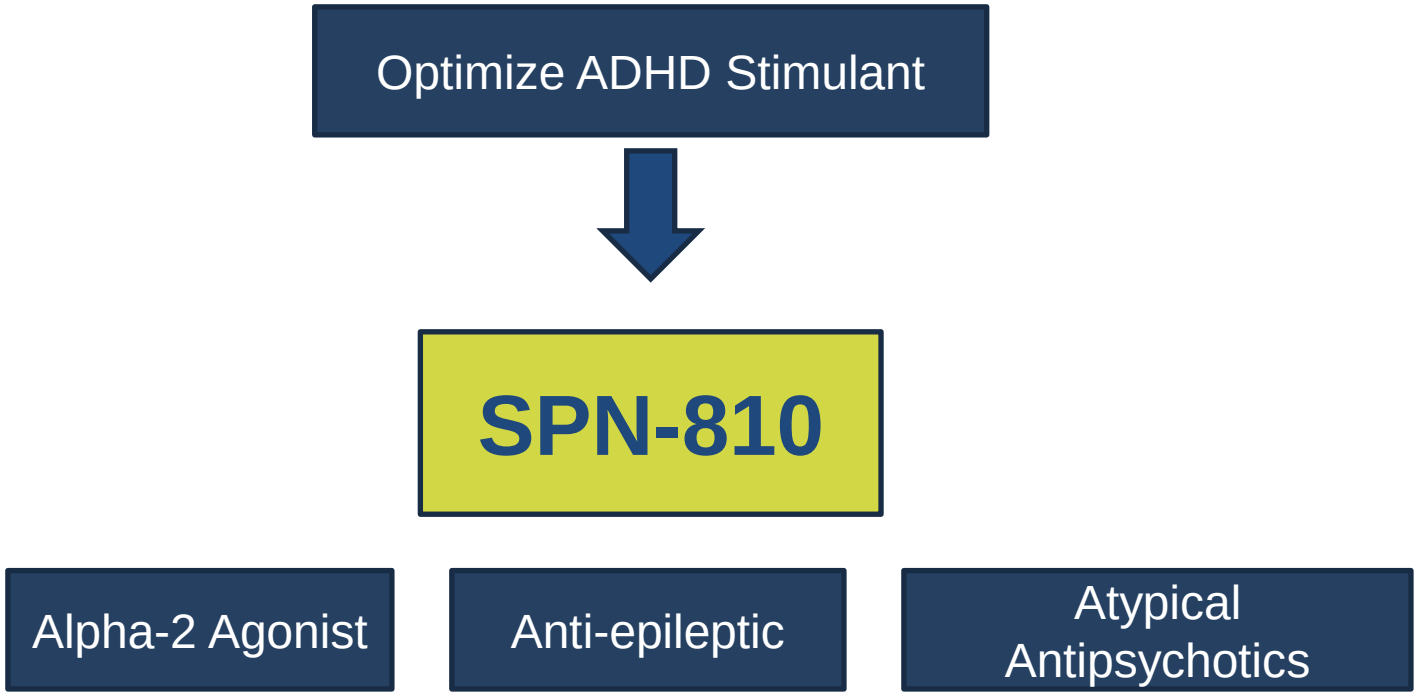
SPN-810: Promising Candidate for Impulsive Aggression Treatment



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SPN-810 Development Program

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SPN-810 Phase IIa Demonstrated Proof of Concept for IR Molindone in Patients with ADHD and Conduct Problems

- IR molindone, dosed three times per day
- Primary Objective:
  - Evaluate safety and tolerability
- Well-tolerated with results suggesting high dose most effective

	Children <30 kg (mg / day)	Children ≥ 30 kg (mg / day)
Group 1	5	10
Group 2	10	20
Group 3	15	30
Group 4	20	40

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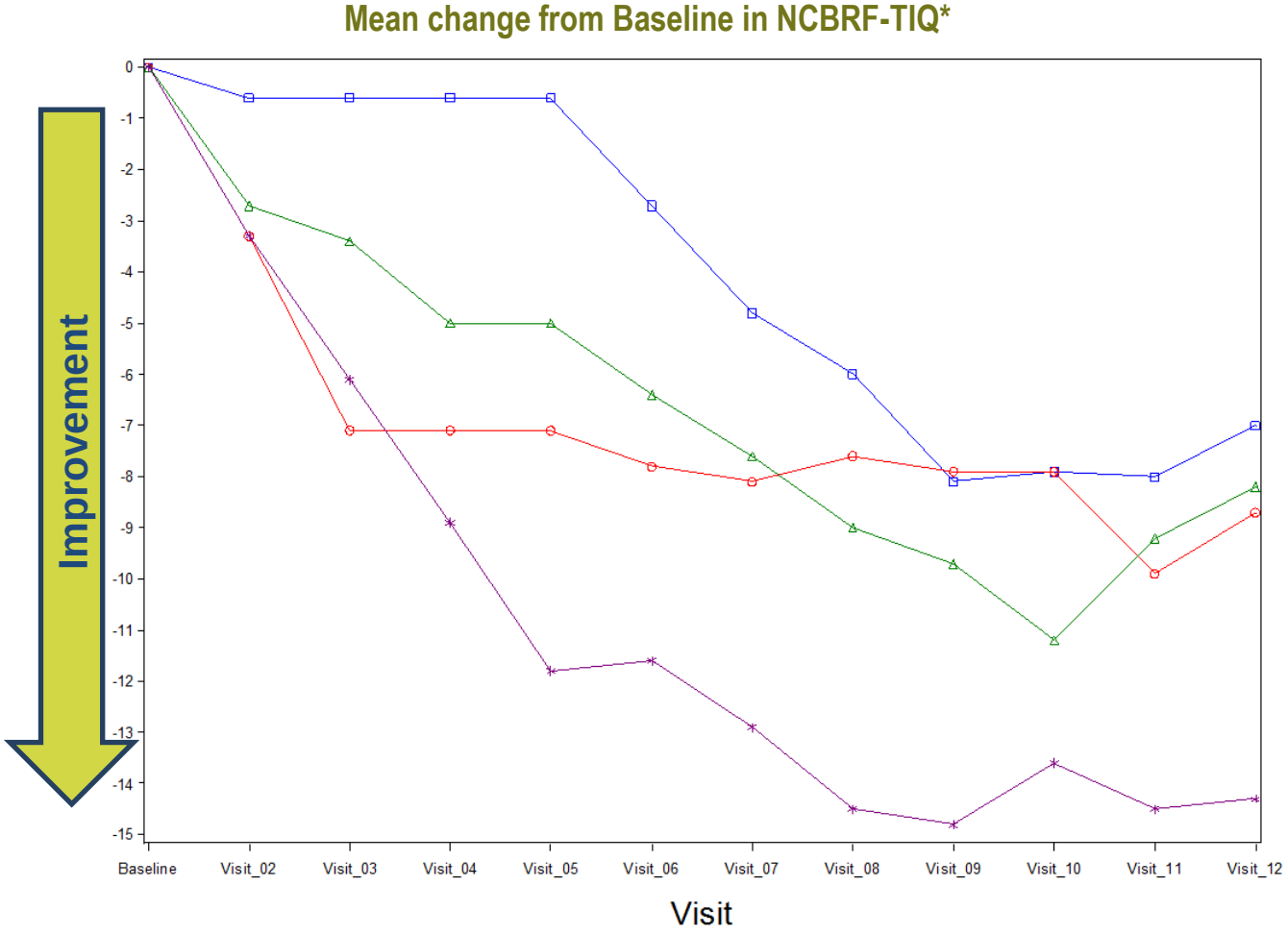
SPN-810 Phase IIa Demonstrated Proof of Concept for IR Molindone in Patients with ADHD and Conduct Problems

Group 1 (mg / day)

Group 2 (mg / day)

Group 3 (mg / day)

Group 4 (mg / day)



* Nisonger Child Behavior Rating Form – Typical IQ

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SPN-810 Phase IIb Study Demonstrated Proof of Concept for Extended Release Formulation in Impulsive Aggression in ADHD

- Extended release molindone
- Randomized, double-blind, placebo-controlled, multicenter
- 6–12 year old patients with Impulsive Aggression co-morbid with ADHD
- Primary endpoint: change from baseline to endpoint (Visit 10) in R-MOAS* ratings.
- Optional six-month open-label extension

	Children < 30 kg (mg/day)	Children ≥ 30 kg (mg/day)
Low Dose	12	18
Medium Dose	24	36
High Dose	36	54

* Retrospective modified overt aggression scale

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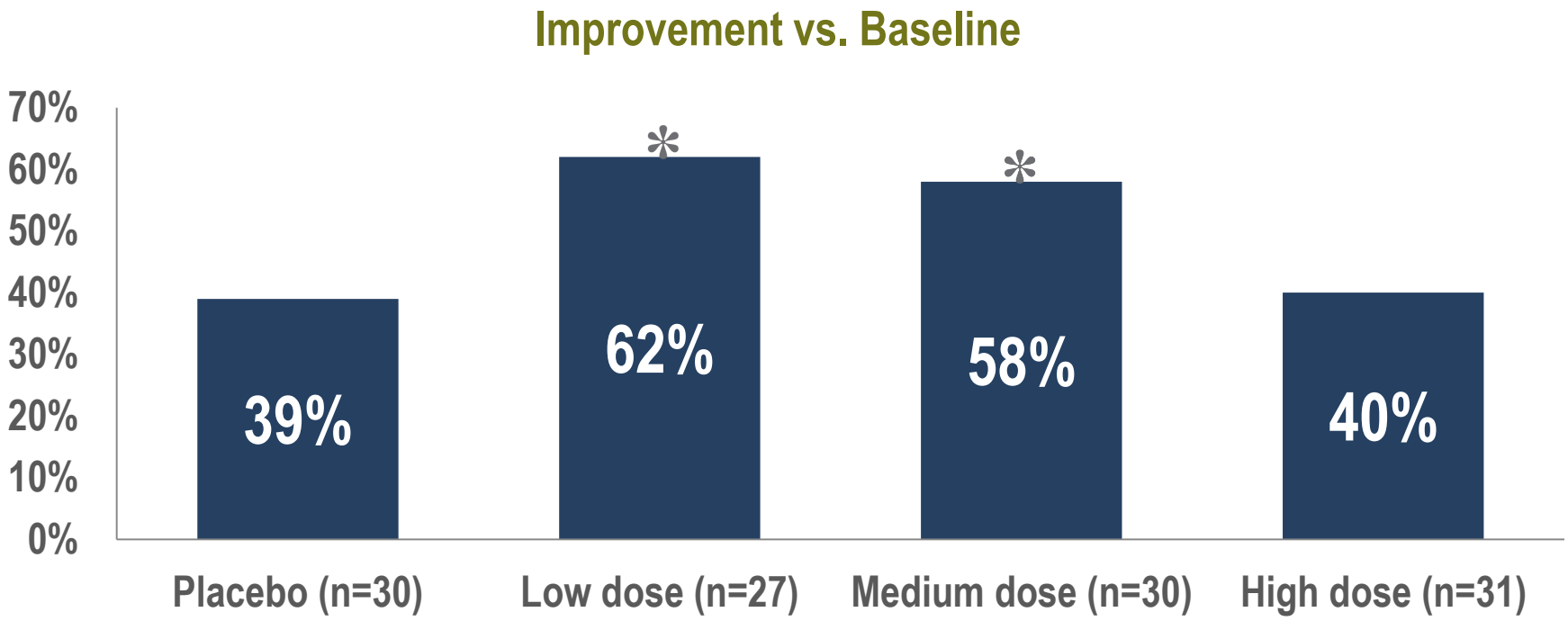
SPN-810 Phase IIb Demonstrated Greater Improvement from Baseline[1]

Primary Endpoint: Change from Baseline at Visit 10 in R-MOAS[#] Score
LOCF, ITT Population



[#] Retrospective modified overt aggression scale

[1] Primary Endpoint based on FDA input

* P<0.05 vs. placebo

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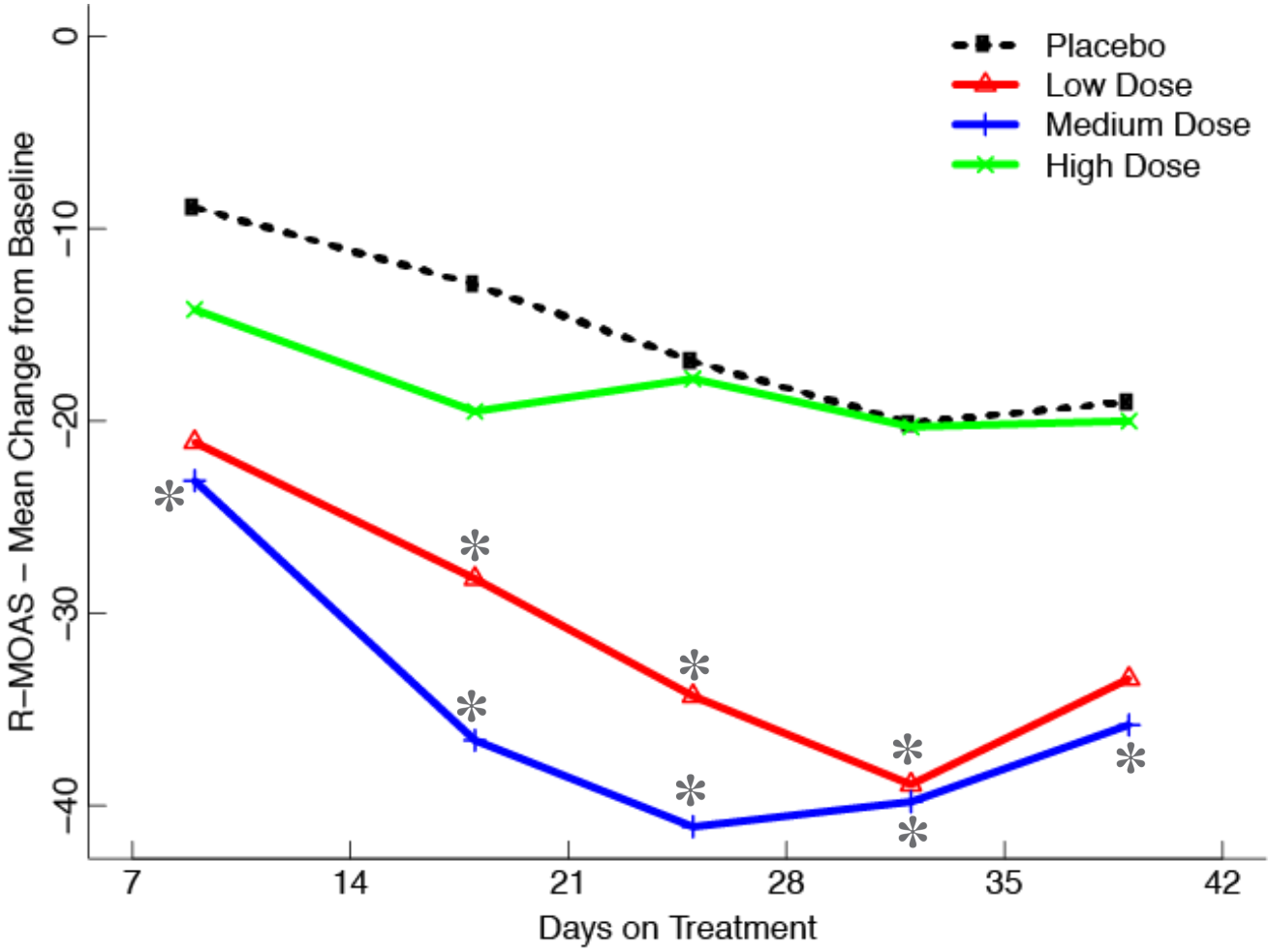
SPN-810 Decreased Impulsive Aggression as Measured by R-MOAS vs. Placebo



*P < 0.05 Treatment vs. Placebo

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SPN-810 Demonstrated Improved Remission Rate at End of Study[1]

R-MOAS	Placebo (n=30)	Low Dose (n=27)	Medium Dose (n=30)	High Dose (n=31)
Subjects Remitted	6 (20%)	14 (52%)	12 (40%)	10 (32%)
P-value for Remission Rate		**0.009**	**0.043**	0.276

P significant at $p < 0.05$

Remission: RMOAS≤10

[1] Primary Endpoint before FDA input

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SPN-810 Was Well-Tolerated

Most Common Adverse Events* (*Reported by ≥ 5% of Subjects in one or more treatment groups*)	Placebo (n=31) N (%)	All Treatment (n=90) N (%)
Headache	4 (13%)	9 (10%)
Sedation	2 (7%)	8 (9%)
Somnolence	1 (3%)	2 (2%)
Abdominal Pain	1 (3%)	5 (6%)
Increased Appetite	1 (3%)	7 (8%)
Decreased Appetite	0	5 (6%)
Fatigue	0	3(3%)
Abnormal Weight Gain	0	1 (1%)
Extrapyramidal Symptoms (EPS)		
Dystonia	0 (0)	2 (2%) [Severe]
Akathisia	1 (3.2%) [Mild]	0 (0)
Dyskinesia	0 (0)	1 (1%) [Moderate]

*There is no statistically significant difference in the rate of incidence of AEs between the placebo arm and all active treatment groups combined

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SPN-810 Demonstrated Low Levels of Weight Gain and Minimal Prolactin Increases

Change from Baseline

	Placebo (n=31) Mean (SD)	Low (n=29) Mean (SD)	Medium (n=30) Mean (SD)	High (n=31) Mean (SD)
Weight Gain (kg)	0.10 (1.225)	0.93 (1.105)	0.93 (1.286)	0.57 (1.153)
BMI (kg / m^2)	0.03 (0.610)	0.45 (0.538)	0.51 (0.644)	0.31 (0.583)
Prolactin (ng / mL)	0.180 (3.4200)	3.588 (6.3359)	10.154 (10.4524)	10.096 (12.1115)

3.2–20 ng / mL considered normal prolactin levels in children*

*WebMD

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Supernus Developed and Validated a Proprietary Tool for Measuring Impulsive Aggression

- FDA requested measurement of frequency of Impulsive Aggression events
  - Does not exist in currently available tools
- Developed psychometrically valid and reliable instrument through robust development / validation process for Phase III
  - Qualitative research (behavior identification / selection)
  - Quantitative research / validation

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Supernus Developed and Validated a Proprietary Tool for Measuring Impulsive Aggression

- Quantitative research / tool validation
  - 103 total subjects (caregivers of likely target pediatric patients)
  - Determined logical and valid model with scoring methodology driven by 15 behaviors (out of 30)
  - Results highly correlated to existing scales including:
    - Nisonger Child Behavior Rating Form – Typical IQ (NCBRF-TIQ)
    - Retrospective-Modified Overt Aggression Scale (R-MOAS)
    - Caregiver Global Impression of Change (CGIC)

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SPN-810 Phase III Study Design

Study	Population	Primary Objective*	Study Duration	Treatment Duration	Dose Range[1]	No. of Subjects	Status
P301	Pediatric (6-12 years)	Efficacy	10 weeks	6 weeks	Placebo 18mg 36mg	291 Randomized	Enrolling
P302	Pediatric (6-12 years)	Efficacy	10 weeks	6 weeks	Placebo 18mg 36mg	291 Randomized	Enrolling

*Primary Endpoint : Change in IA behavior frequency

[1]Predefined interim analysis of P301 completed September 2017

- Both trials proceeding to completion with 1:1 randomization to 36mg dose and placebo

Primary Endpoint in Phase III

- Percent change in frequency of Impulsive Aggression behaviors per 7 days in maintenance period relative to baseline period
  - In the intent-to-treat (ITT) population calculated over the number of days with reported Impulsive Aggression diary data
- Measured using newly-developed, validated, proprietary electronic diary tool

Secondary Endpoints in Phase III

- Clinical Global Impression - Improvement Scale (CGI-I)
- Clinical Global Impression - Severity Scale (CGI-S)
- Child Health Questionnaire (CHQ-PF28)
- Parenting Stress Index (PSI-SF)
- SNAP-IV Rating Scale

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Extensive Safety Monitoring in Phase III

- Adverse events
- Extrapyramidal symptoms (EPS) scales
  - Simpson-Angus Scale
  - Barnes Akathisia Scale
  - Abnormal Involuntary Movement Scale
- Clinical laboratory tests
  - Hematology, chemistry and urinalysis
  - Insulin, prolactin, triglycerides
- ECGs
- Vital signs
- Columbia Suicide Severity Rating Scale (C-SSRS)

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SPN-810 Commercial Opportunity

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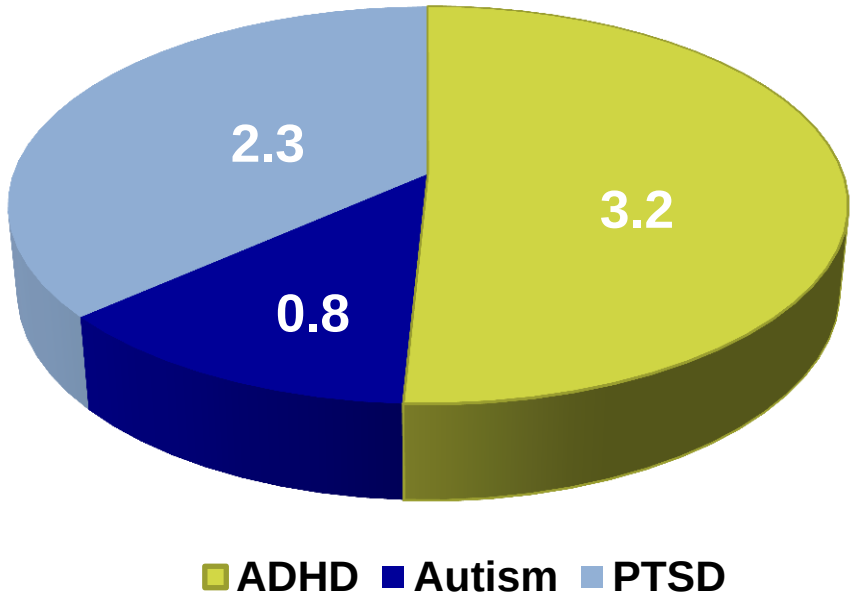
SPN-810: Novel Product for IA

Granted Fast Track Development Designation

1st Expected to be First Product Approved to Treat IA

2017 Two Ongoing Phase III Trials

Market Opportunity
+$6.3B



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Extensive Market Research Conducted to Date on SPN-810

Study	Timing	Sample
Qualitative Opportunity Assessment Research (n=24)	1Q14	▪ KOLs (n=6) ▪ Community Physicians (n=18)

Extensive Market Research Conducted to Date on SPN-810

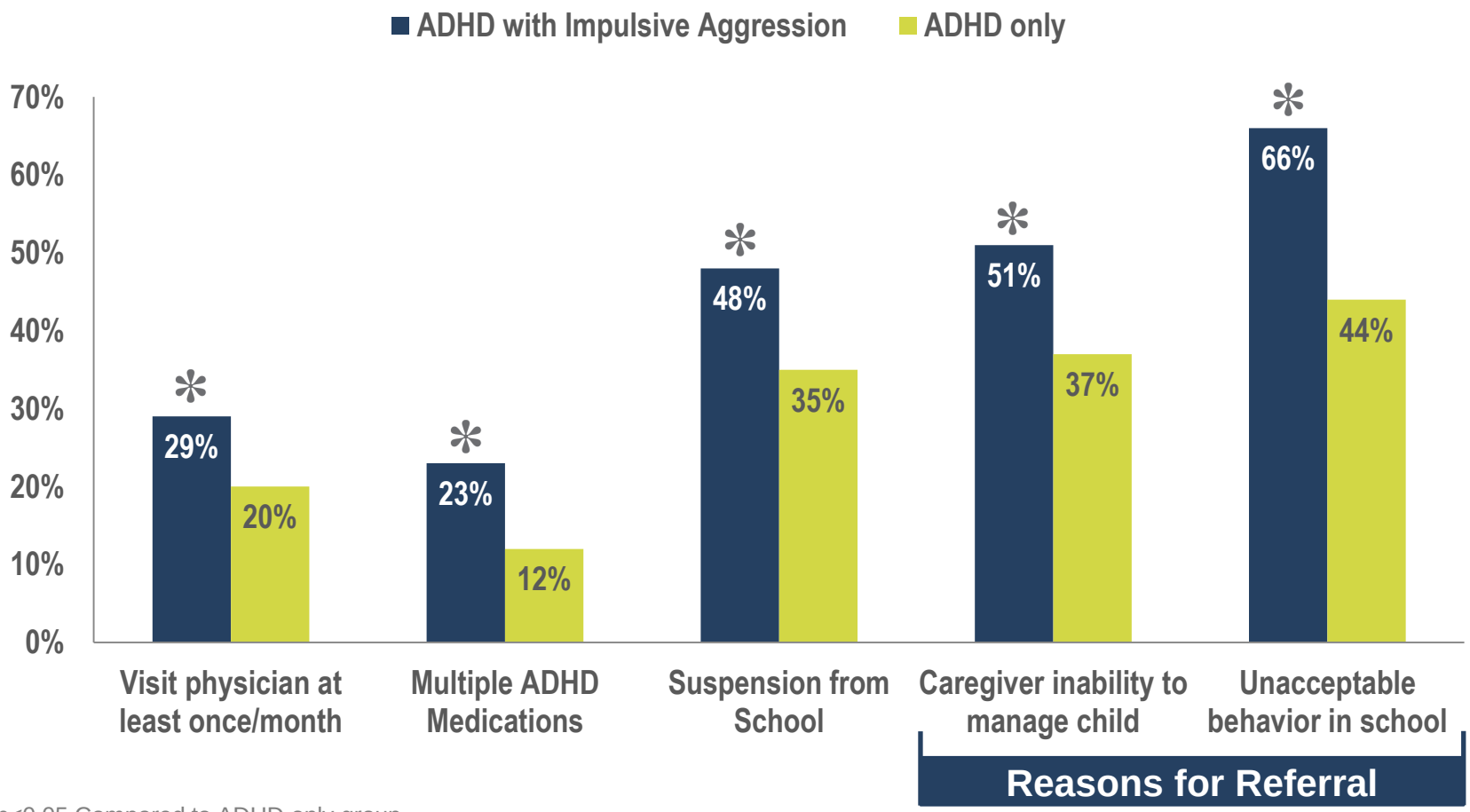
Study	Timing	Sample
Qualitative Opportunity Assessment Research (n=24)	1Q14	▪ KOLs (n=6) ▪ Community Physicians (n=18)
Target Product Profile Research (n=45)	4Q14	▪ ADHD/Aggression KOLs (n=7) ▪ Community Physicians (n=20) ▪ Payers (n=18) • Managed Care Pharmacy Directors (n=10) ○ Representing National, Regional and Local Plans ○ <1 MM to >10 MM lives covered • PBM Pharmacy Directors (n=2) • Medicaid Programs (n=2) • Other (n=4)

Extensive Market Research Conducted on SPN-810

Study	Timing	Sample
Qualitative Opportunity Assessment Research (n=24)	1Q14	▪ KOLs (n=6) ▪ Community Physicians (n=18)
Target Product Profile Research (n=45)	4Q14	▪ ADHD/Aggression KOLs (n=7) ▪ Community Physicians (n=20) ▪ Payers (n=18) • Managed Care Pharmacy Directors (n=10) ○ Representing National, Regional and Local Plans ○ <1 MM to >10 MM lives covered • PBM Pharmacy Directors (n=2) • Medicaid Programs (n=2) • Other (n=4)
Quantitative Market Sizing and Demand (n=182)	2Q15	**1,092 Patient Records; 182 Physicians** ▪ Child Psychiatrists (n=120; 720 records) ▪ Developmental / Behavioral Pediatricians (n=30; 180 records) ▪ Child Neurologists (n=32; 192 records)

Supernus® Pharmaceuticals

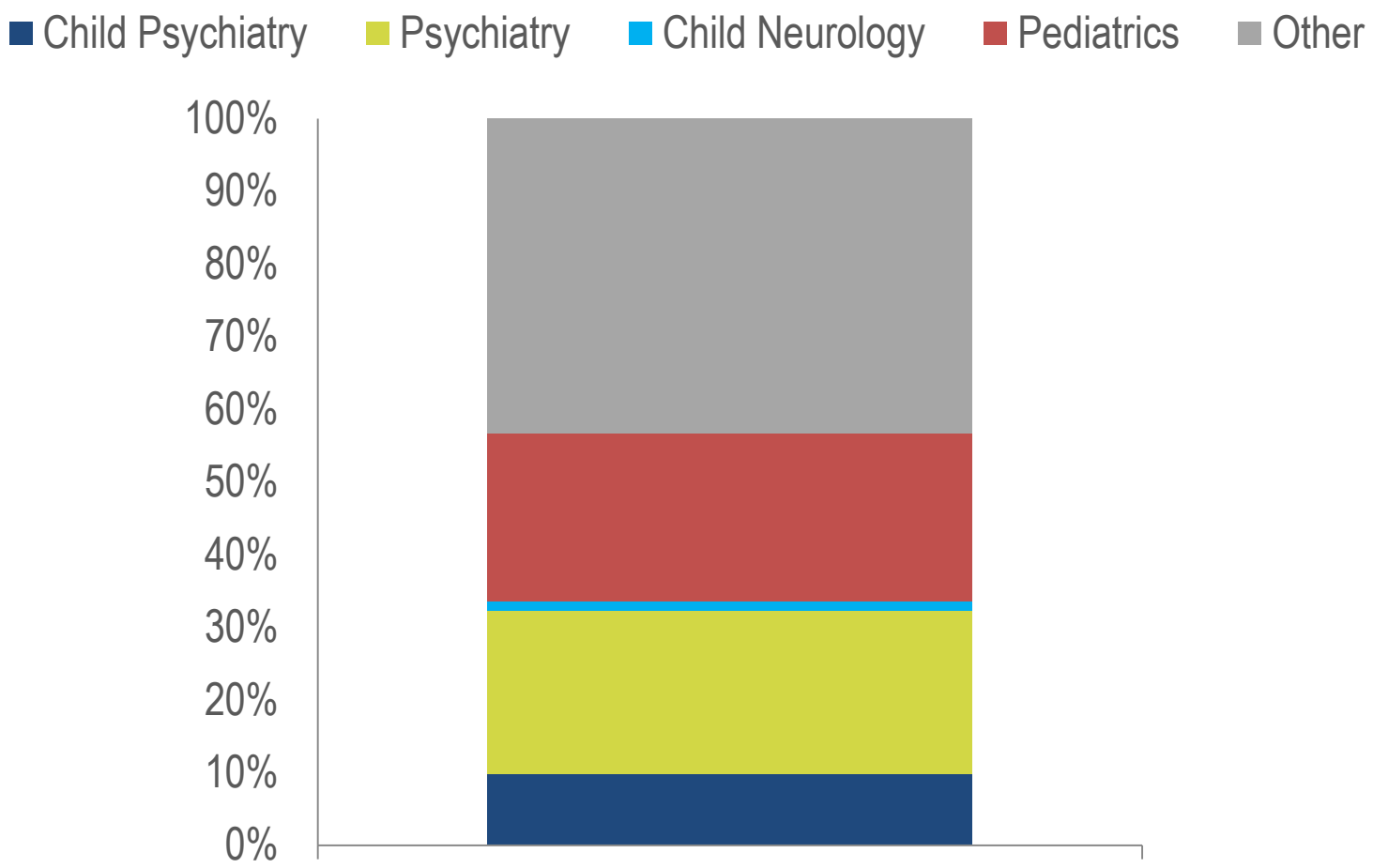
Impulsive Aggression in ADHD is a Significant Concern for Physicians, Parents and Caregivers



* p<0.05 Compared to ADHD only group

SPN-810 Market Sizing and Demand Study; April 2015

Initial Focus: Child Psychiatry, Child Neurology, Psychiatry and High Volume ADHD Pediatricians



SHA MAT JAN 15 based on physician prescribing for all ADHD products contained in USCs 64500 and 64700

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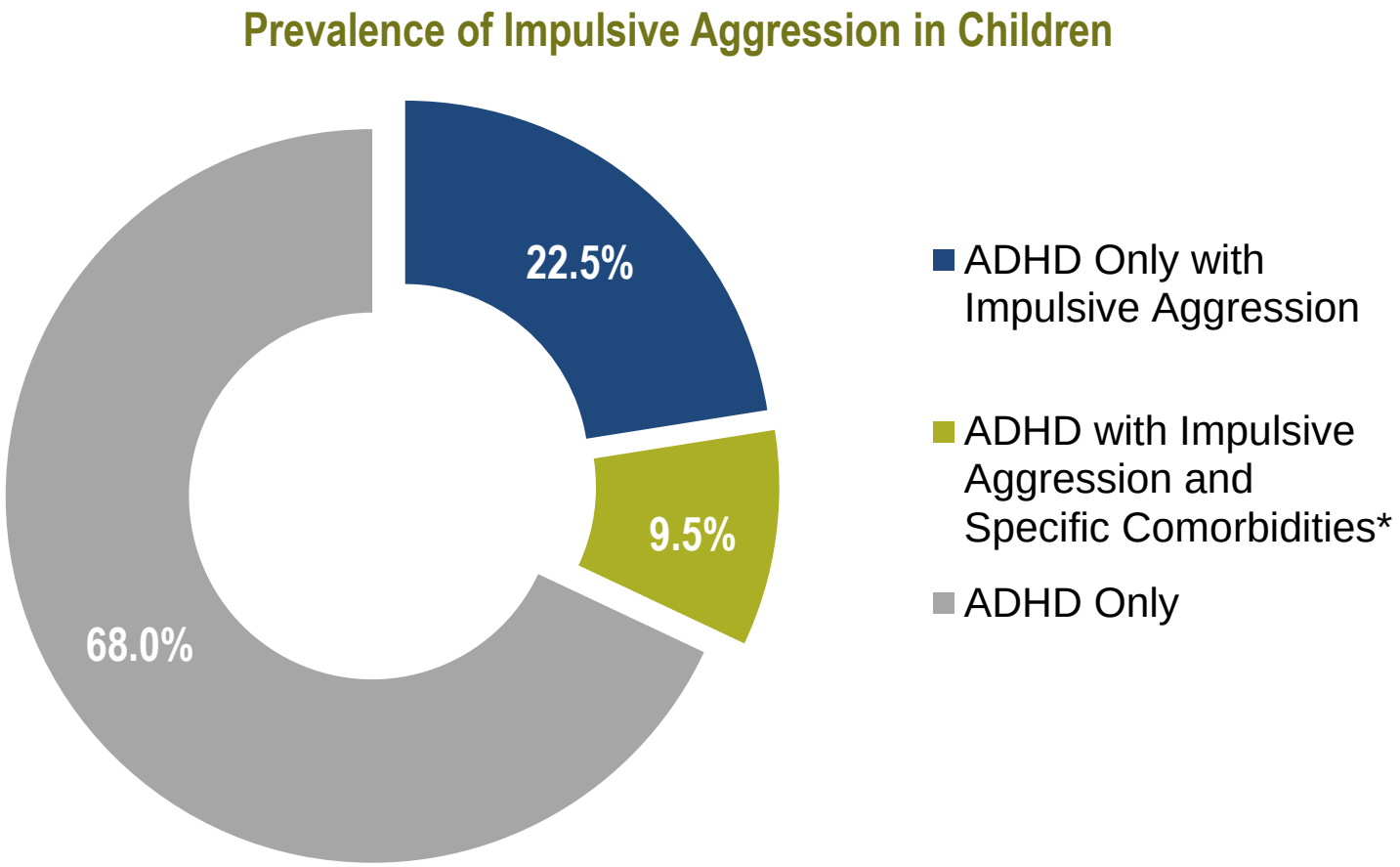
Addressable Child and Adolescent ADHD Prescriptions

Addressable ADHD Prescriptions		
	2014	Projected at Launch Year
Child Psychiatrists	5.0 Million	5.8 Million
Psychiatrists	4.9 Million	5.6 Million
Child Neurologists	0.8 Million	0.9 Million
Pediatricians (Top Deciles)	6.1 Million	6.9 Million
Total	16.8 Million	19.2 Million

SHA MAT JAN 15 based on TRx by physician for all ADHD products contained in USCs 64500 and 64700 for age ≤ 20; 3% YOY launch year Projection

Supernus® Pharmaceuticals

Prevalence of Impulsive Aggression in Addressable ADHD Population is 22.5–32%



SPN-810 Market Sizing and Demand Study; April 2015;
*Specific co-morbidities: autism, epilepsy, IQ<70, neurological disorders, bipolar disorder, schizophrenia

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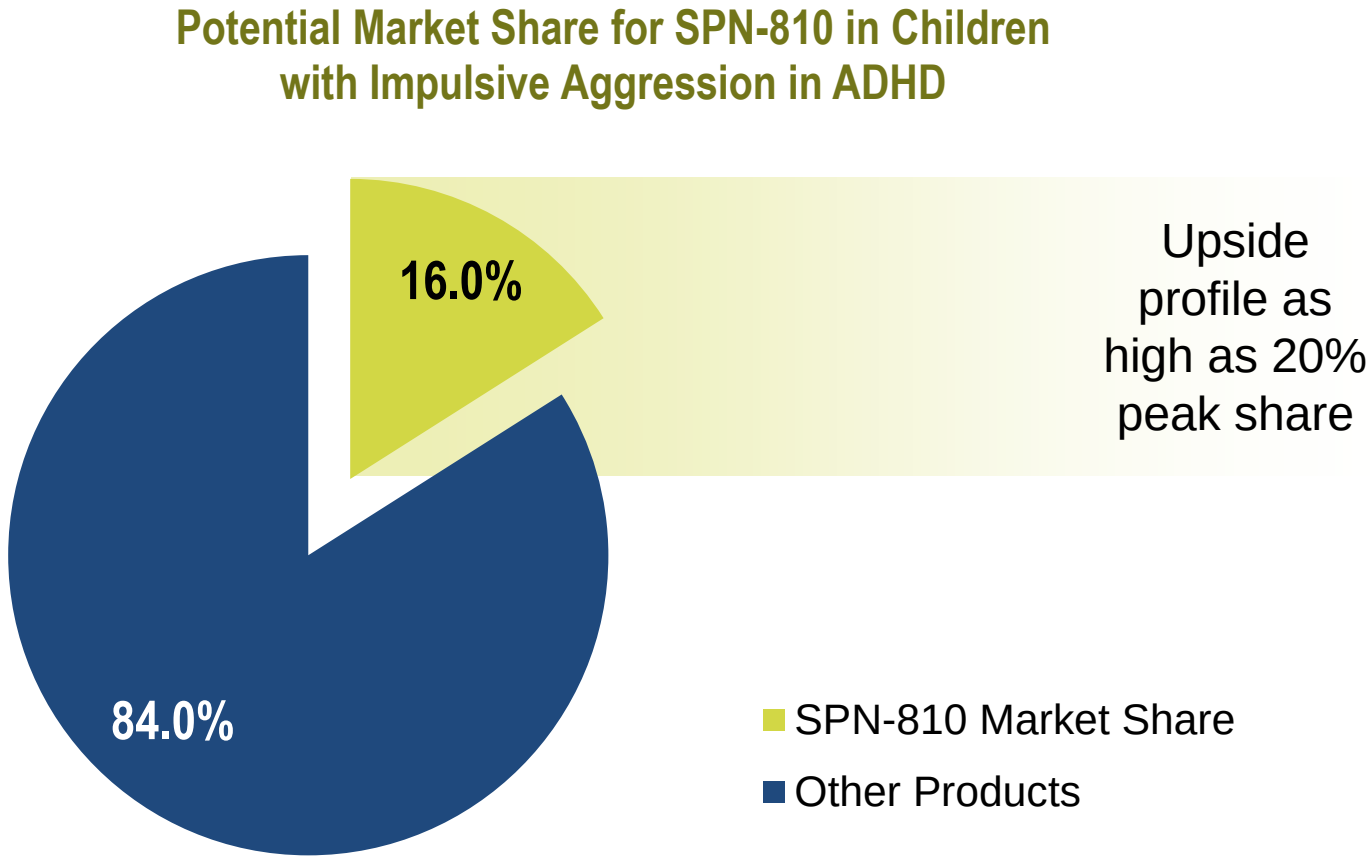
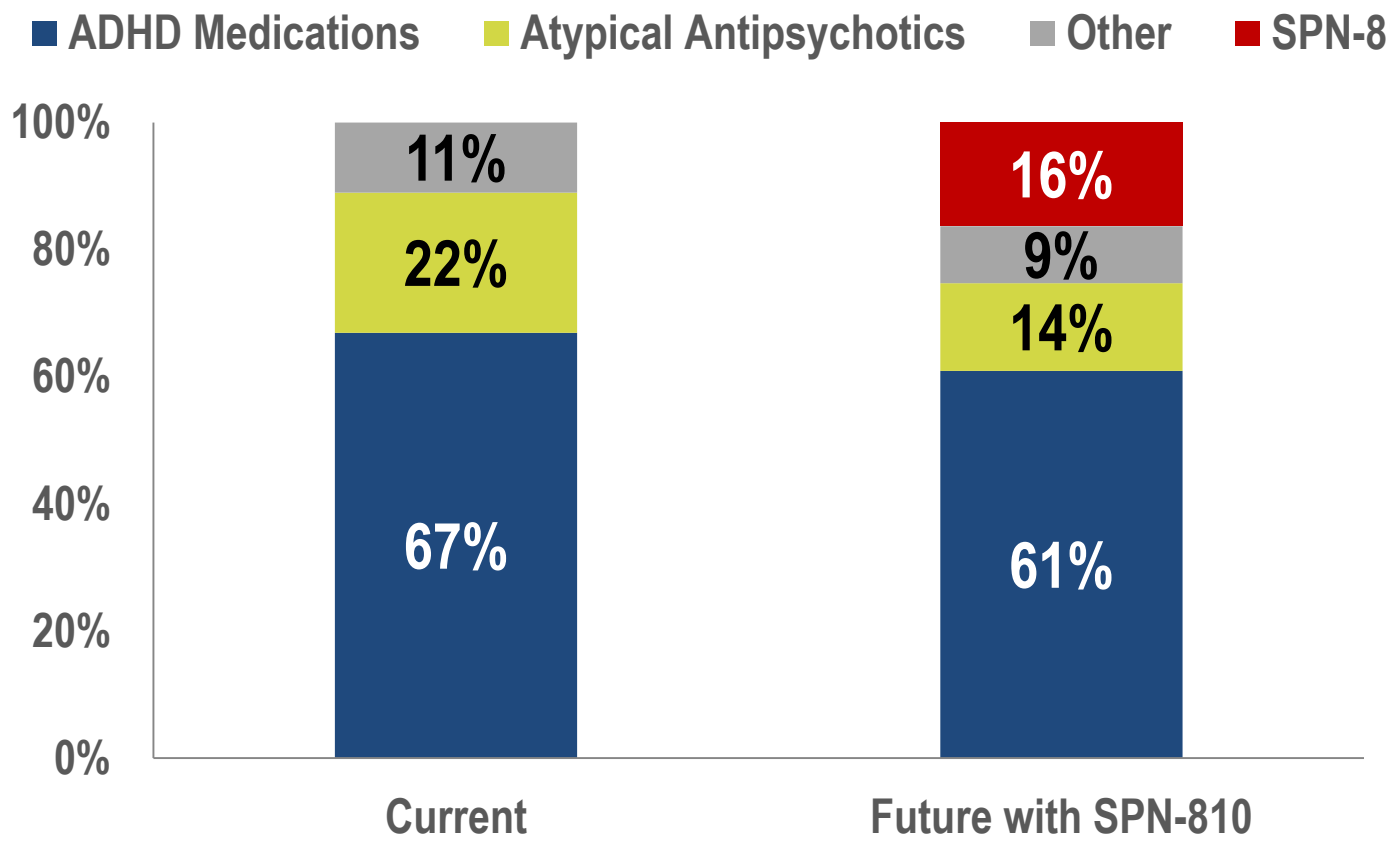
Market Research Suggests 16-20% Market Share for SPN-810 in Impulsive Aggression in ADHD



SPN-810 Market Sizing and Demand Study; April 2015

Research Suggests Half of SPN-810 Prescriptions as Replacement for Existing Atypical Antipsychotics



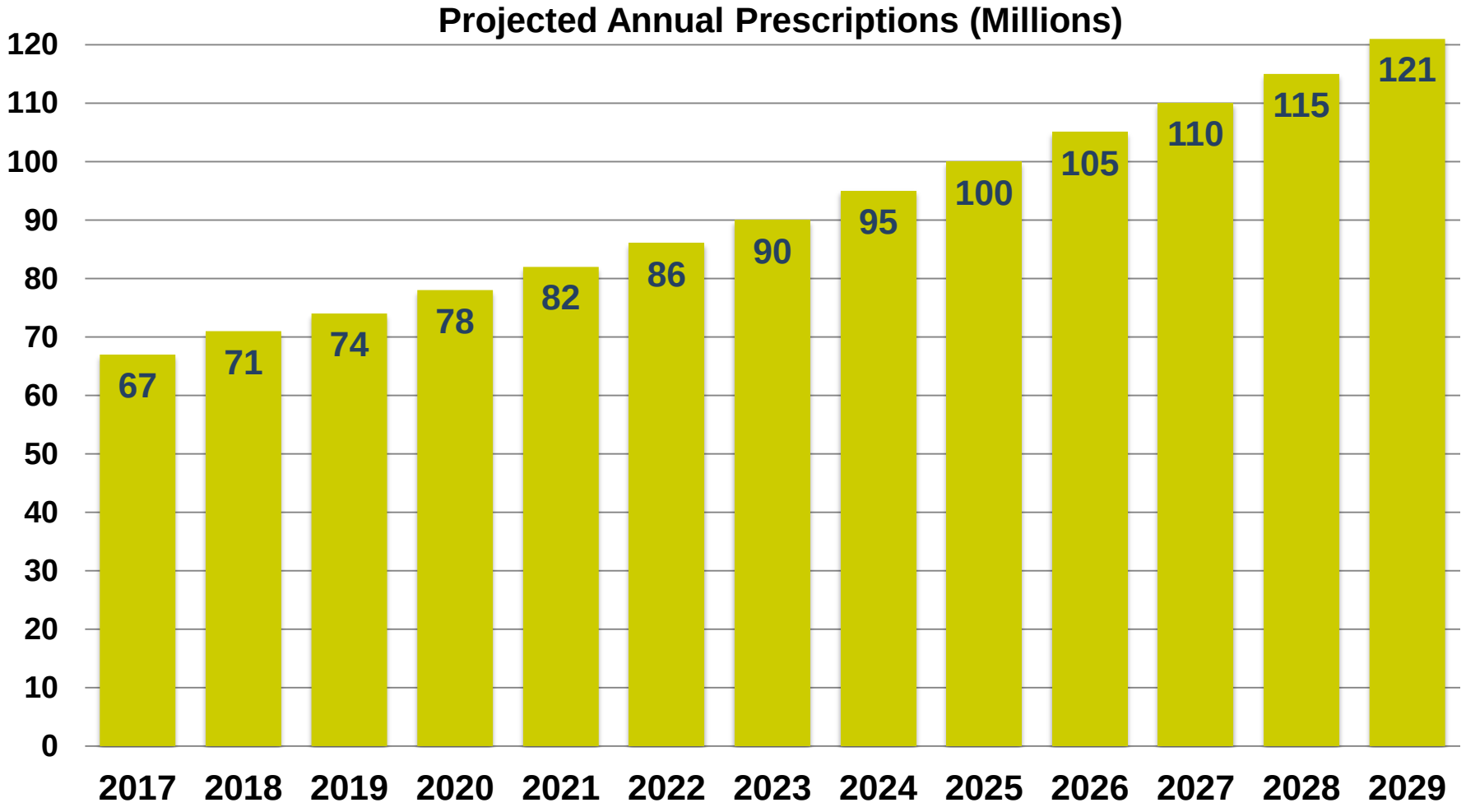
Assumed coverage by Medicaid and by most Insurance plans as a Tier 3 brand

Standard ADHD Medications included stimulants and alpha-2 agonists

SPN-810 Market Sizing and Demand Study; April 2015

Supernus® Pharmaceuticals

ADHD Market Opportunity in the U.S



Source - IMS NPA and Company Estimates

Supernus® Pharmaceuticals

SPN-810 Market Opportunity for IA in ADHD

	Percent	Prescriptions in Peak Year
ADHD Market Prescriptions		95 - 110 Million
Child and Adolescent ADHD Prescriptions Child Psychiatrists, Child Neurologists, Psychiatrists, and Top Pediatrician Deciles		24 - 28 Million
Prevalence of Impulsive Aggression	22.5 - 32%	5.4 - 9.0 Million
	Peak Market Share	**SPN-810 Potential Prescriptions**
SPN-810 Peak Demand	**16 - 20%**	**0.9 - 1.8 Million**

SPN-810 Market Sizing and Demand Study (April 2015); Assumes prevalence and demand from quantitative research are applicable to high ADHD pediatrician prescribers, and peak market share at 3–5 years post launch

SPN-810

A Potential Billion Dollar Product for Supernus

	Potential Gross Revenue
ADHD	$515 - $1,050 Million
Autism and PTSD	$590 - $720 Million
Total at Peak	$1,105 - $1,770 Million

+

Other Impulsive Aggression Opportunities:

Schizophrenia, Bipolar, Alzheimer's, Oppositional Defiant Disorder, etc.

SPN-812
Clinical Perspective

Keith Saylor, Ph.D., Sc.M.
Licensed Clinical Psychologist
President and CEO of NeuroScience, Inc.

From Investor Day – June 2015

Supernus® Pharmaceuticals

ADHD is the Most Common Neurobehavioral Disorder in Children

- Characterized by persistent and developmentally excessive levels of activity, impulsivity, and inattention
  - Cause difficulty at school, at home, or with friends
- Three primary presentations
  - Inattentive presentation
  - Hyperactive / impulsive presentation
  - Combined presentation (includes both)

Supernus® Pharmaceuticals

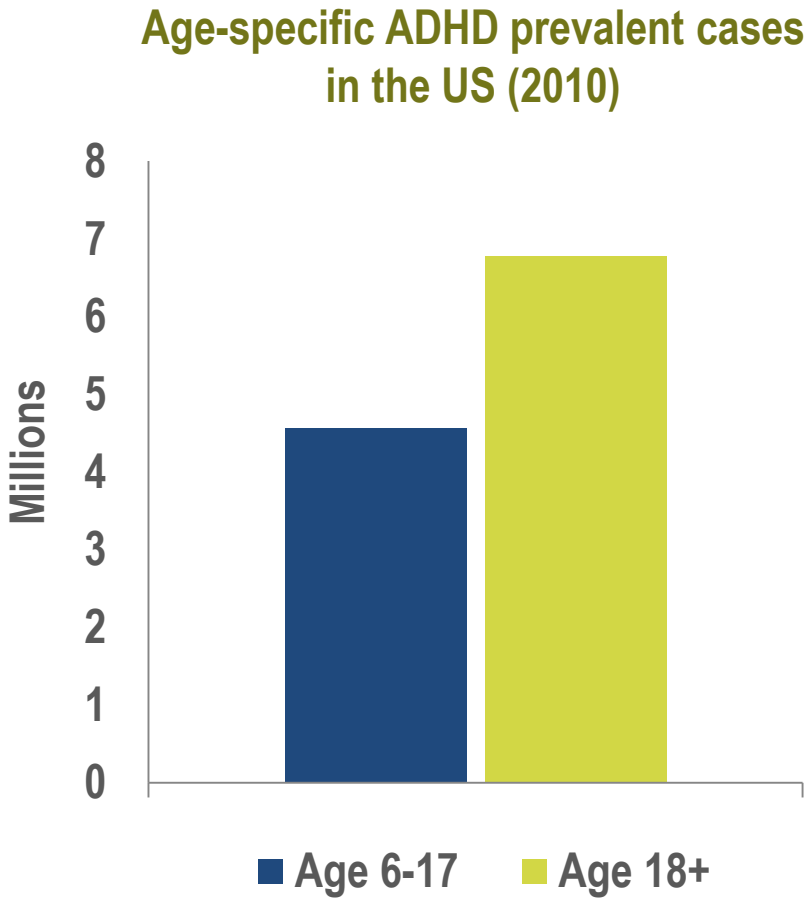
Diagnosis and Treatment of ADHD

- Intensively studied for over 50 years
- No single test to diagnose ADHD
  - Reliable and valid interviews suffice
- Treatment consistent for decades
  - Medication
  - Behavior therapy
  - Combination
- Discontinuing treatment usually results in relapse

Supernus® Pharmaceuticals

ADHD is Prevalent Among Children, Adolescents, and Adults

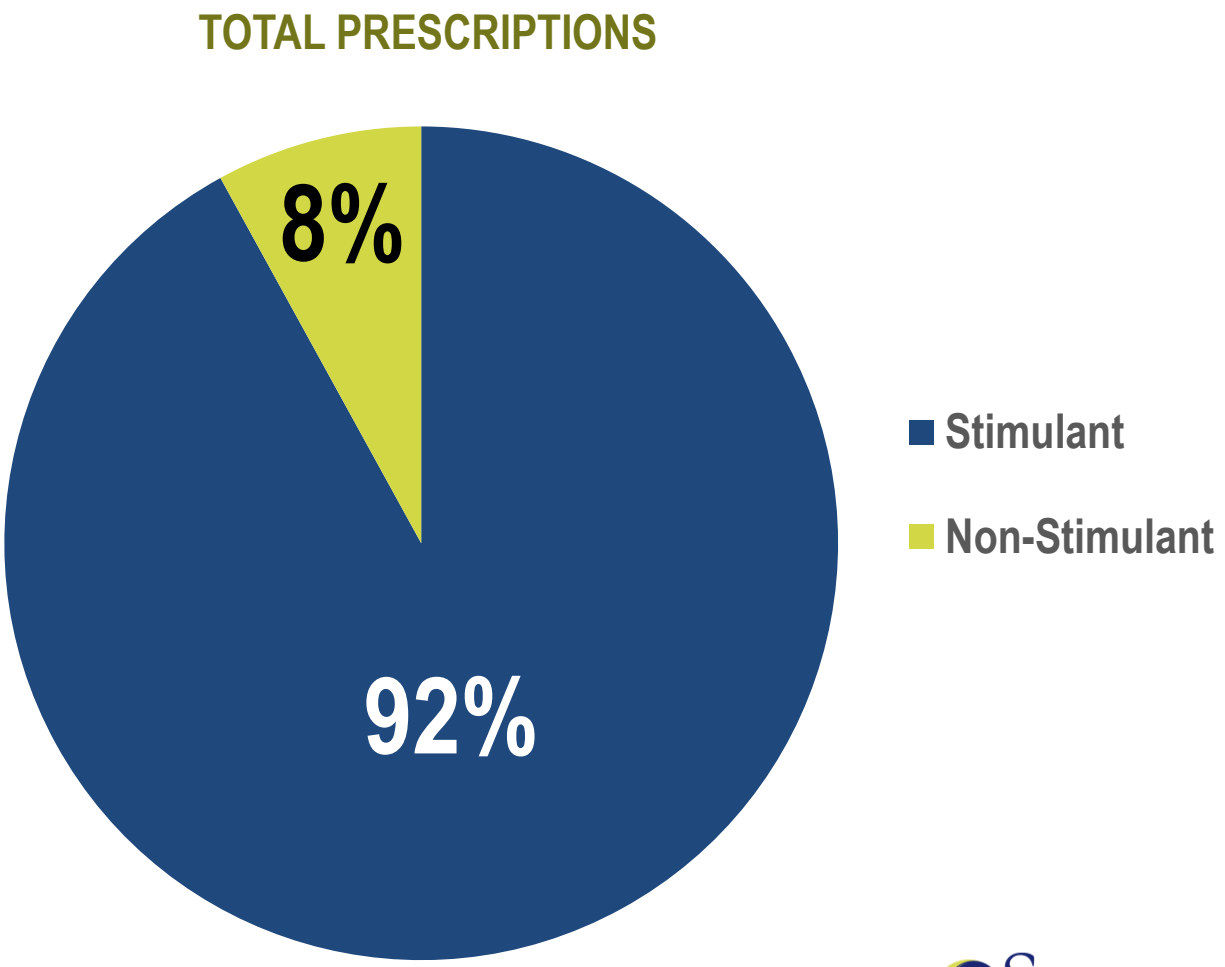
- Prevalence:
  - 11% of children in US
- 6% of children in US are on medication for ADHD
- 60% of children with ADHD will continue with symptoms as adults
- Childhood treatment results in fewer problems as adults



Centers for Disease Control "Trends in the Parent-Report of Health Care Provider-Diagnosed and Medicated ADHD: United States, 2003–2011; WebMD; Datamonitor

Supernus® Pharmaceuticals

Stimulants Remain Standard of Care for ADHD



Source: SHA TRx data, December 2014

Mix of Short and Long-Acting Treatment Options for ADHD

Approved Stimulants

- Amphetamines
- Methylphenidate
- Long acting and immediate release options

Approved Non-Stimulants

- Selective norephinephrine reuptake inhibitor
- Alpha-2 agonists (long acting)

Source: SHA TRx data, Year 2014

Supernus® Pharmaceuticals

Stimulants Have Disadvantages

- Inadvisable to use for specific co-morbidities
  - Substance use disorder
  - Tics / Tourette's / Obsessive Compulsive Disorder (OCD)
  - Anxiety
- Stimulant resistance
- Prescribing challenges
- Side effects: appetite loss, abdominal pain, headaches, sleep disturbances
- Potential for diversion leading to misuse, abuse, and/or dependence
- Parent concerns

Supernus® Pharmaceuticals

Non-Stimulants Address Gaps in Stimulant Use

- Monotherapy where stimulants not an option
  - Patients who can’t have a stimulant
  - Patients who can’t tolerate a stimulant
  - Parents who prefer not to give a stimulant
- Adjunctive to stimulant
  - Permit a lower dose of stimulant
  - Extends duration of coverage when stimulants wear off

Supernus® Pharmaceuticals

Strattera and Intuniv are Most Commonly Prescribed Non-Stimulants for ADHD

	Strattera® (atomoxetine)	Intuniv® (guanfacine extended release)
Manufacturer	Eli Lilly	Shire
Date of Approval	2002	2009
Generic Equivalent	Expected 2017	Introduced December 2014
Population	Adults and Children	Children Only
Indication	Monotherapy Only	Monotherapy and Adjunctive with Stimulants
Mechanism of Action	Norepinephrine Reuptake Inhibitor	Alpha-2 Agonist

Supernus® Pharmaceuticals

Strattera and Intuniv are Most Commonly Prescribed Non-Stimulants for ADHD

	Strattera (atomoxetine)	Intuniv (guanfacine extended release)
Efficacy	• Less effective than stimulants • Can take weeks to see effect	Less effective than stimulants
Most Common Side Effects	• Upset stomach • Decreased appetite • Nausea or vomiting • Dizziness • Tiredness • Mood swings	• Sleepiness • Dizziness • Tiredness • Dry mouth • Trouble sleeping • Irritability • Low blood pressure • Vomiting • Nausea • Slow heart rate • Stomach pain
Potential Risks	Blackbox for suicidality Risks for liver failure, cardiovascular, GI (nausea and vomiting)	Risks of hypotension, insomnia, sedation
Formulation / Dosage / Administration	Can't be diluted in water / sprinkled on food	Can't be crushed

Other Non-Stimulants Used as Last Resort

- Kapvay (extended release clonidine hydrochloride)
  - Side effects limit use
- Off-label use in ADHD
  - Tricyclic antidepressants
    - Multiple significant side effects
  - Wellbutrin (buproprion)
    - Less effective
  - Nuvigil/Provigil (armodafinil / modafinil)
    - Stimulant-like side effects
    - Limited efficacy

Supernus® Pharmaceuticals

Opportunity Exists for New, Effective Non-Stimulant Options for Treatment of ADHD

- ADHD is most common neurobehavioral disorder
- Stimulants are effective ADHD treatments, but have significant side effects and prescribing issues
- Current non-stimulant options are limited
- New non-stimulant choices are welcome
  - Efficacy
  - Quicker onset of efficacy
  - Improved side effect profile

Supernus® Pharmaceuticals

SPN-812 Development Program

Supernus® Pharmaceuticals

SPN-812: Novel Non-Stimulant ADHD Product

- Viloxazine hydrochloride
  - Norepinephrine reuptake inhibitor
- Once-daily oral extended-release product
- New Chemical Entity (NCE)
  - Five year market exclusivity
  - Previously marketed outside the US as an antidepressant
- Building strong IP portfolio with expirations from 2029-2033
- Emerging clinical profile points to a well differentiated ADHD product
  - A highly effective non-stimulant with a tolerable side effect profile

Supernus® Pharmaceuticals

SPN-812 Demonstrated Proof of Concept in Adults With ADHD

- Primary objective
  - Determine safety of immediate release formulation
- Secondary objective
  - Determine efficacy
  - Explore single dose and steady state pharmacokinetics
- Efficacy measures
  - Investigator-rated and self-rated Conners' Adult ADHD Rating Scale (CAARS) Total ADHD Symptom Score
  - Clinical Global Impression - Improvement (CGI-I)

SPN-812 Demonstrated Proof of Concept in Adults With ADHD

- Study Design: Randomized, double-blind, placebo controlled, parallel group
- Duration: 8 weeks, including screening (2 weeks) and titration (1 week)
- Subjects: 26 randomized, 24 completed per treatment group
- Sites: 5 U.S.
- Primary Efficacy Endpoint: Reduction from baseline in investigator-rated CAARS score

Supernus® Pharmaceuticals

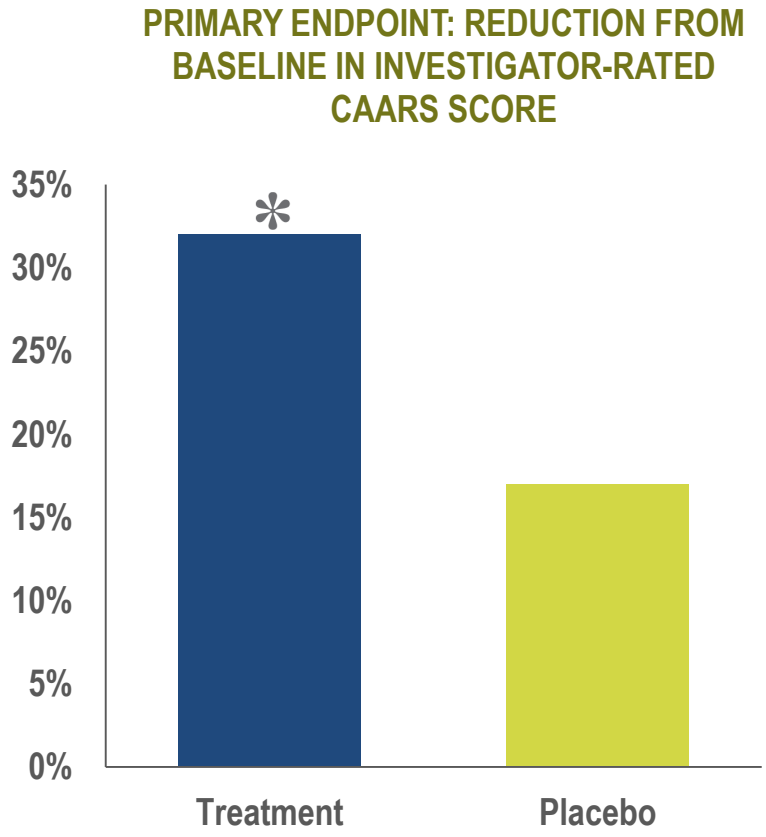
SPN-812 Showed Significant Symptom Reduction Compared to Placebo

Efficacy

- Showed statistically significant symptom reduction vs. placebo

Safety

- Well-tolerated
- Safety profile consistent with prior viloxazine data
- Most common AEs: nausea, decreased appetite, headache, insomnia, and dry mouth
- No SAE or death occurred during the study



* p<0.05; After 5 weeks on treatment

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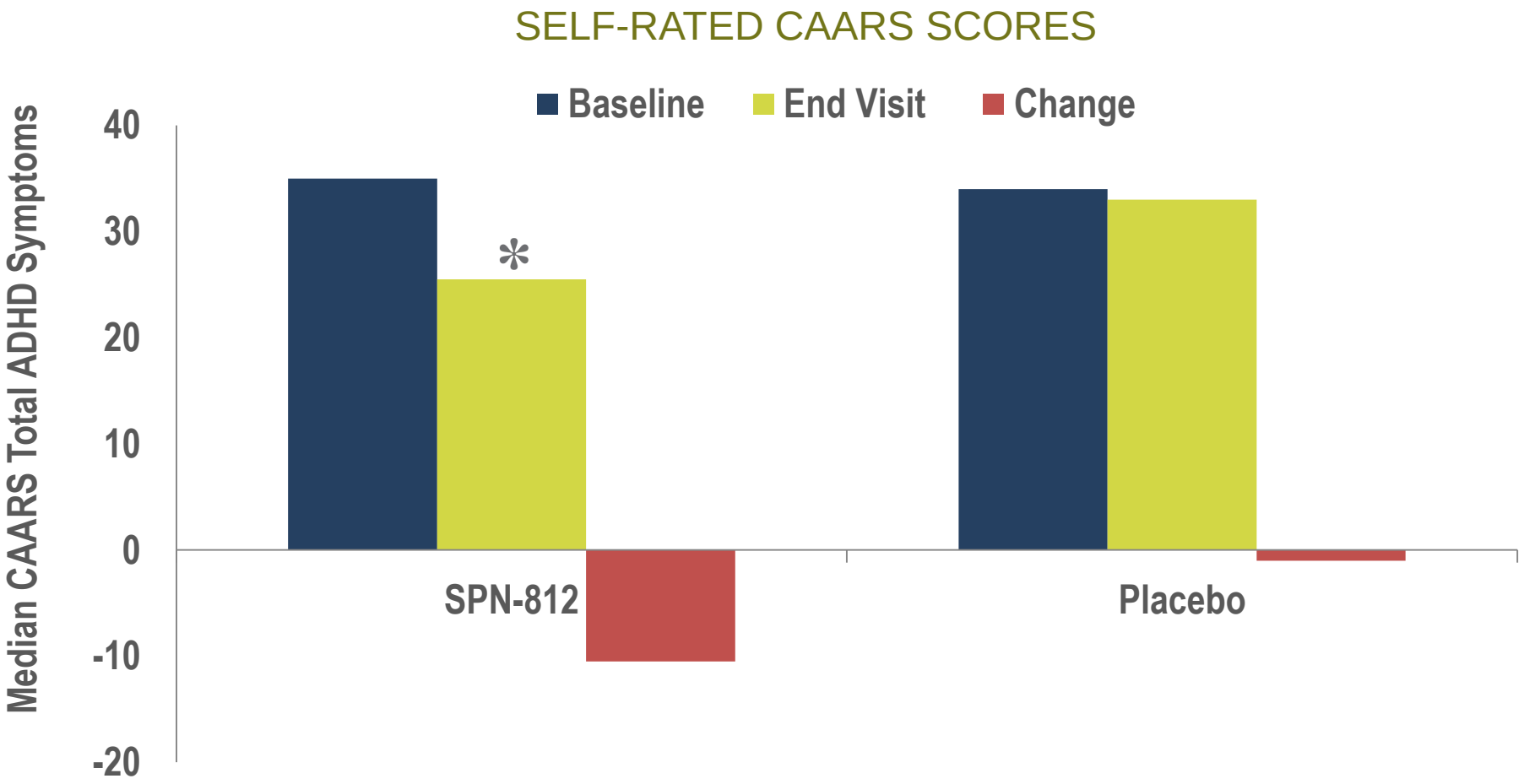
SPN-812 Showed Significant Symptom Reduction Compared to Placebo



* p=0.0349

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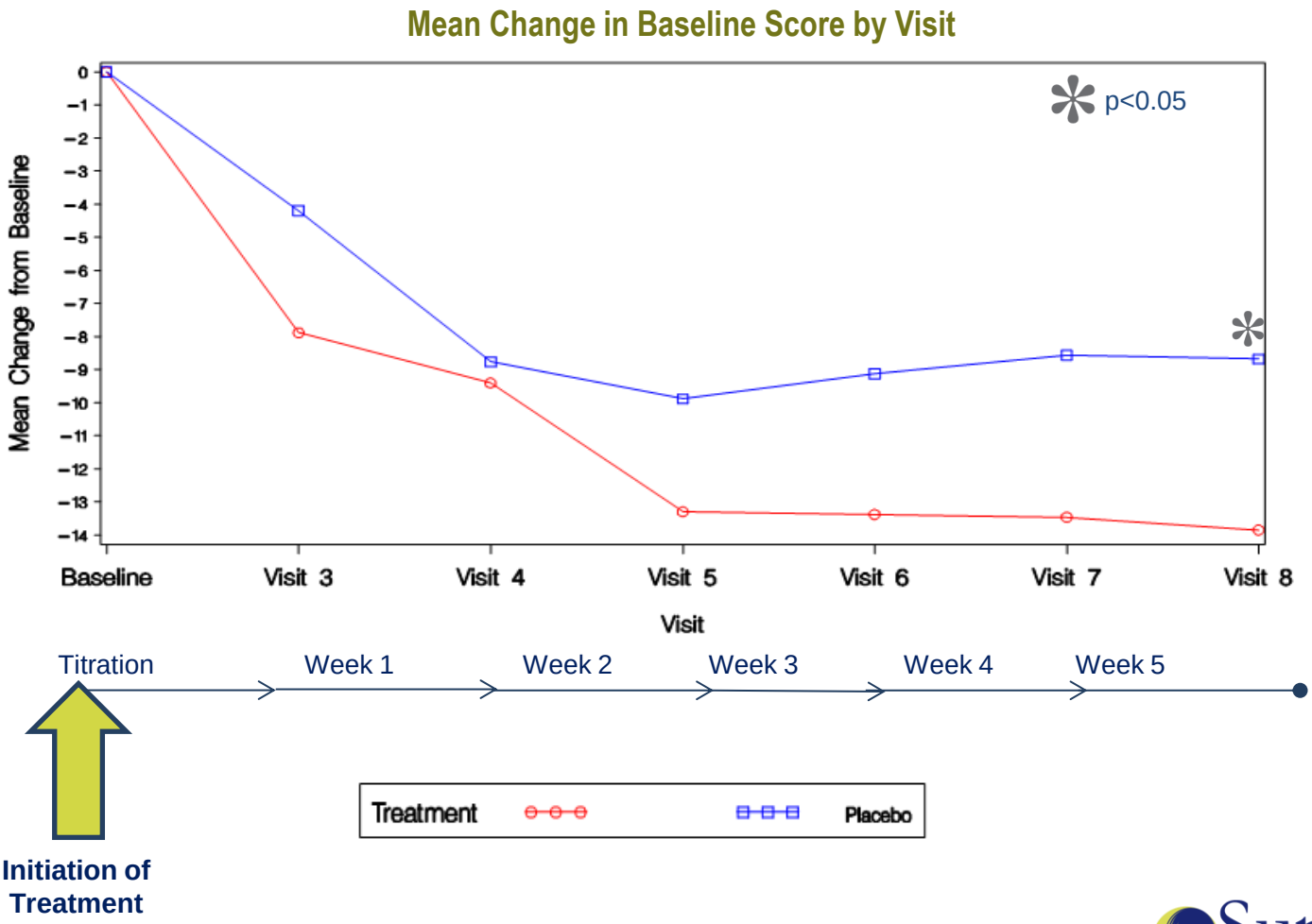
SPN-812 Effect Evident Early in Treatment



SPN-812 Phase IIb Design

- **Objectives:**
  - Assess effect in reducing symptoms of ADHD in children aged 6-12 years
  - Evaluate safety and tolerability
- **Primary Endpoint**:
  - Change from baseline to End of Study in the ADHD-RS-IV total score
- **Design:**
  - Double-blind, placebo-controlled, multicenter, dose-ranging study
    - Placebo, 100/200/300/400mg
  - Monotherapy
  - 222 subjects randomized
  - 3 weeks titration (100mg/week), 5 weeks treatment
  - Rollover to Open-Label Extension Study

Supernus® Pharmaceuticals

Three SPN-812 Doses Met Primary Endpoint

Primary Analysis
Change from baseline in ADHD-RS-IV Total Score (ITT Population with LOCF)

Statistics	400 mg N=44	300 mg N=47	200 mg N=46	100 mg N=45	Placebo N=24	
LS Mean	-19.0	-18.6	-18.4	-16.7	-10.5	End of Study
Effect Size	0.63	0.60	0.55	0.46		
P-value	**0.021***	**0.027***	**0.031***	**0.089**		

* At end of study all SPN-812 doses except the 100 mg dose are statistically significant compared to placebo at α = 0.05 level.

ITT = Intent To Treat
LOCF = Last Observation Carried Forward

Supernus® Pharmaceuticals

SPN-812 Was Well Tolerated

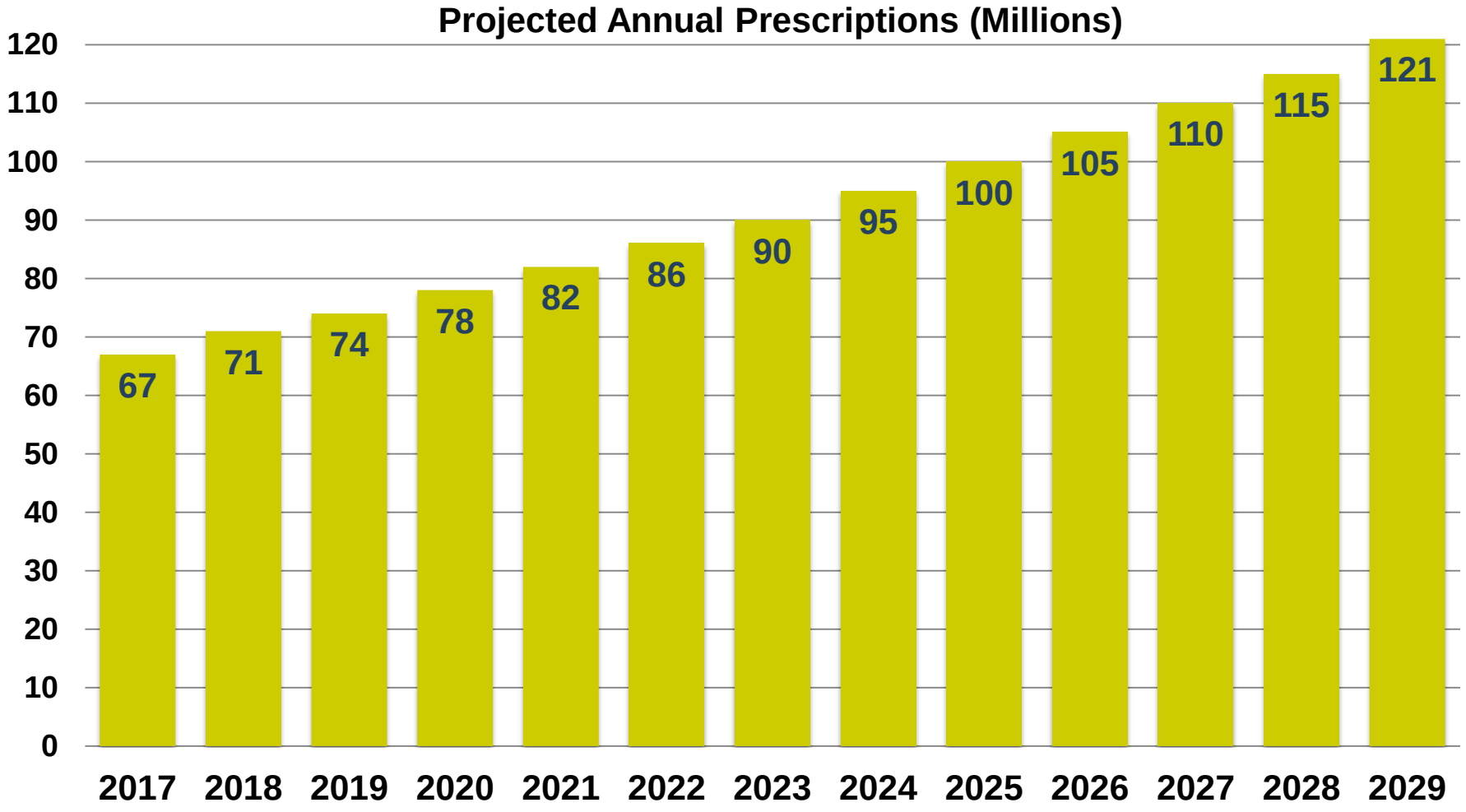
Percentage of Patients with Related AEs, >5%		SPN-812 ER			
Adverse Event (AE)	Placebo N=24	100 mg N=48	200 mg N=48	300 mg N=48	400 mg N=49
Somnolence	0	14.6	20.8	20.8	24.5
Decreased appetite	8.3	10.4	12.5	8.3	16.3
Headache	0	4.2	10.4	6.3	12.2
Insomnia	0	6.3	4.2	6.3	6.3
Nausea	0	4.2	2.1	8.3	4.1
Fatigue	0	4.2	4.2	2.1	10.2
Irritability	0	2.1	8.3	4.2	2.0
Weight decreased	0	0	0	0	8.3
Discontinuations Due to AEs	0	8.3	6.3	2.1	10.2

Supernus® Pharmaceuticals

SPN-812 Commercial Opportunity

Supernus® Pharmaceuticals

ADHD Market Opportunity in the U.S



Source - IMS NPA and Company Estimates

Supernus® Pharmaceuticals

SPN-812

A Potential Billion Dollar Product for Supernus

		Estimated Prescriptions in Peak Year
ADHD Market Prescriptions		**90 - 100 Million**
	Peak Market Share %	**SPN-812 Potential Prescriptions**
SPN-812 Peak Demand	**3 - 5%**	**2.7 - 5.0 Million**
SPN-812 Peak Gross Revenue		**$1.6 - 3.0 Billion**

Source: IMS NPA, Company Research and Estimates – Assumes peak at 3-5 years post launch

Oxtellar XR®
Bipolar Disorder

Supernus® Pharmaceuticals

Oxtellar XR® : Novel Product for Bipolar

50% Use of Oxcarbazepine in Psychiatry

1st Expected to be Only Oxcarbazepine Product Approved to Treat Bipolar

2017 Investigator-Initiated Trial Started in 3Q

Market Opportunity
+53 Million Prescriptions

Class of Drugs	% of Prescriptions
Antiepileptics	34
Antipsychotics	29
SSRI's	15
SNRI's	6
Antimania	6
Other Antidepressants	6
Benzodiazepines	4
Total	100

Source: IMS 2016

SSRI = Selective serotonin reuptake inhibitor
SNRI = Serotonin & norepinephrine reuptake inhibitor

Supernus® Pharmaceuticals

Positioned For Continued Strong Growth

Strong Portfolio in Neurology

Potential Peak Sales for Oxtellar XR® and Trokendi XR® >$500M

Innovative Late Stage Portfolio in Psychiatry

SPN-810 : First Treatment to be Developed for Impulsive Aggression

SPN-812 : Highly Effective and Well Tolerated Non-Stimulant

Oxtellar XR : Novel Product for Bipolar Disorder

Supernus® Pharmaceuticals