# Supernus Pharmaceuticals

## SPN-812 P304 Phase III Topline Data

**March 28, 2019**

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# SPN-812

## Novel Non-Stimulant ADHD Product Candidate

- Viloxazine hydrochloride
  - Serotonin norepinephrine modulating agent (SNMA)
  - New Chemical Entity (NCE) with five year market exclusivity
  - Previously marketed outside the U.S. as an antidepressant
- Building strong IP with expirations from 2029-2033
- Clinical data point to a well-differentiated ADHD product
- Continue to target NDA submission 2H 2019, and if approved, launch 2H 2020

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# SPN-812
## Phase III Studies Status

| | P301<br>N = 477 | P303<br>N = 313 | P302<br>N = 310 | P304<br>N = 297 |
|---|---|---|---|---|
| **ADHD Patients** | 6-11 years | 6-11 years | 12-17 years | 12-17 years |
| **Daily Doses** | 100 mg<br>200 mg | 200 mg<br>400 mg | 200 mg<br>400 mg | 400 mg<br>600 mg |
| **Status** | Completed | Completed | Completed | Completed |

# SPN-812 P304 Phase III Study Design

- Monotherapy in adolescent ADHD patients 12-17 years old
- Primary Endpoint
  - Change from baseline on ADHD-RS-5 scale compared to placebo
- Secondary Endpoints
  - Clinical Global Impression - Improvement (CGI-I) scale
  - Conners 3rd Edition - parent, composite T-score
  - Weiss Functional Impairment Rating Scale - parent report (WFIRS-P)
- Evaluate safety & tolerability

# SPN-812 P304 Topline Results

## Executive Summary

- Data confirm positive results from P301, P302, and P303 Phase III studies

  - 400 mg reached statistical significance on:
    - Change versus baseline in ADHD Rating Scale 5, p-value = 0.0082
    - Effect size of 0.66
    - CGI-I secondary endpoint, p-value = 0.0051
    - Hyperactivity/Impulsivity subscale, p-value = 0.0484
    - Inattention subscale, p-value = 0.0042
    - Sensitivity analysis confirms primary analysis

# SPN-812 P304 Topline Results
## Executive Summary

- Data confirm positive results from P301, P302, and P303 Phase III studies
  - 400 mg shows fast onset of action
    - Statistical significance as early as 2 weeks
- Higher dose of 600 mg did not reach statistical significance
    - Narrowly missed on primary endpoint with p-value of 0.0712
    - May indicate a dosage plateauing effect
    - Not needed for approvability of NDA
- Consistent favorable tolerability and safety profile
  - Low incidence of AE's across both doses (400 mg and 600 mg)
  - Low discontinuation rates due to AE's of 4.0% - 5.1%

# SPN-812 P304 Phase III Topline Results

## Primary Analysis of ADHD-RS-5 based on MMRM (ITT Population)

| Visit | Statistics | Placebo (N=96) | 400 mg (N=99) | 600 mg (N=97) |
|---|---|---|---|---|
| Baseline | Mean | 38.8 | 41.2 | 39.8 |
| | | | | |
| Week 7 (EOS) | LS Mean | -13.2 | -18.3 | -16.7 |
| | **p-value** | | **0.0082** | **0.0712** |

MMRM = Mixed Model for Repeated Measure ITT = Intent to Treat EOS = End of Study

# SPN-812 P304 Phase III Topline Results

## Efficacy on 400 mg starting in week 2

| Visit | Statistics | Placebo (N=96) | 400 mg (N=99) | 600 mg (N=97) |
|---|---|---|---|---|
| Baseline | Mean | 38.8 | 41.2 | 39.8 |
| | | | | |
| Week 1 | LS Mean | -5.0 | -6.7 | -7.7 |
| | p-value | | 0.2460 | 0.0664 |
| Week 2 | LS Mean | -7.8 | -12.1 | -10.9 |
| | p-value | | 0.0063 | 0.0456 |
| Week 3 | LS Mean | -9.7 | -14.7 | -13.6 |
| | p-value | | 0.0035 | 0.0238 |
| Week 4 | LS Mean | -11.7 | -16.2 | -13.8 |
| | p-value | | 0.0119 | 0.2423 |
| Week 5 | LS Mean | -12.7 | -17.2 | -14.9 |
| | p-value | | 0.0100 | 0.1983 |
| Week 6 | LS Mean | -13.5 | -18.4 | -16.8 |
| | p-value | | 0.0065 | 0.0690 |
| **Week 7 (EOS)** | LS Mean | -13.2 | -18.3 | -16.7 |
| | **p-value** | | **0.0082** | **0.0712** |

MMRM = Mixed Model for Repeated Measure ITT = Intent to Treat EOS = End of Study

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# SPN-812 P304 Phase III Topline Results

**Sensitivity Analysis of ADHD-RS-5 based on ANCOVA at Week 7 (EOS) Confirms Primary Analysis (ITT Population)**

| Visit | Statistics | Placebo (N=96) | 400 mg (N=99) | 600 mg (N=97) |
|---|---|---|---|---|
| Baseline | Mean | 38.8 | 41.2 | 39.8 |
| | | | | |
| Week 7 (EOS) | LS Mean | -13.4 | -17.9 | -16.5 |
| | **p-value** | | **0.0191** | **0.1002** |

ANCOVA = Analysis of Covariance
ITT = Intent to Treat EOS = End of Study

# SPN-812 P304 Phase III Topline Results

## Analysis of Observed Global Improvement Score (CGI-I) at Week 7 (EOS)

| Visit | Statistics | Placebo (N=96) | 400 mg (N=99) | 600 mg (N=97) |
|---|---|---|---|---|
| Baseline | Mean | 4.5 | 4.8 | 4.6 |
| | | | | |
| Week 7 (EOS) | LS Mean | 2.9 | 2.4 | 2.6 |
| | **p-value** | | **0.0051** | **0.0995** |

CGI-S was used as baseline; EOS = End of study

# SPN-812 P304 Phase III Topline Results

## Significant Reduction in Hyperactivity and Inattention for 400 mg

### Analysis in ADHD-RS-5 Inattention and Hyperactivity/Impulsivity Subscales

| Visit | Statistics | Placebo (N=96) | 400 mg (N=99) | 600 mg (N=97) |
|---|---|---|---|---|
| **ADHD-RS-5 Hyperactivity/Impulsivity** | | | | |
| Baseline | Mean | 16.4 | 18.7 | 17.5 |
| Week 7 (EOS) | LS Mean | -6.4 | -8.3 | -7.6 |
| | **p-value** | | **0.0484** | **0.2084** |
| **ADHD-RS-5 Inattention** | | | | |
| Baseline | Mean | 22.4 | 22.5 | 22.3 |
| Week 7 (EOS) | LS Mean | -7.1 | -10.1 | -8.7 |
| | **p-value** | | **0.0042** | **0.1392** |

EOS = End of Study

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# SPN-812 P304 Phase III Topline Results

## 400 mg and 600 mg Well Tolerated

**Number (%) of Patients - Treatment Related AEs with ≥ 5% incidence**

| | Placebo (N=97) | 400 mg (N=100) | 600 mg (N=99) |
|---|---|---|---|
| Somnolence | 3 (3.1) | 13 (13.0) | 17 (17.2) |
| Fatigue | 4 (4.1) | 11 (11.0) | 10 (10.1) |
| Headache | 3 (3.1) | 9 (9.0) | 7 (7.1) |
| Decreased appetite | 2 (2.1) | 6 (6.0) | 6 (6.1) |
| Nausea | 2 (2.1) | 5 (5.0) | 8 (8.1) |
| | | | |
| Discontinuation due to AEs | 1 (1.0) | 4 (4.0) | 5 (5.1) |

AEs = Adverse Events

# SPN-812 Phase III Program
## Executive Summary

- Final Phase III data package for the NDA is robust on 100 mg, 200 mg and 400 mg doses in more than 1,000 children and adolescent patients.
- P304 Fourth Phase III trial
  - Consistent with and confirms results from three successful Phase III trials (P301, P302 and P303) in children and adolescents
- Clinical data point to a well-differentiated ADHD product
  - Strong efficacy with robust statistical significance
  - Efficacy on both Hyperactivity/Impulsivity and Inattention
  - Fast onset of action
  - Very well tolerated
- Continue to target NDA submission 2H 2019, and if approved, launch 2H 2020

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# Positioned For Continued Strong Growth

## Growth Potential for Existing Products

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

## Innovative Late Stage Portfolio in Psychiatry

| | |
|---|---|
| **SPN-812** | **Well Differentiated Novel Non-Stimulant** |
| **SPN-810** | **First Product to be Developed for Impulsive Aggression** |
| **SPN-604** | **Novel Product for Bipolar Disorder** |



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