



Sumitomo Dainippon
Pharma

Innovation today, healthier tomorrows

R&D Meeting

February 28, 2017

Sumitomo Dainippon Pharma Co., Ltd.

Today's Agenda

1. Introduction

Masayo Tada

President and CEO

2. Towards Sustainable Growth

Hiroshi Noguchi, Ph.D.

Senior Executive Vice President and CSO

3. Psychiatry & Neurology Area, Respiratory Area: Pipeline Driving Sustainable Growth

Antony Loebel, M.D.

Executive Officer, Head of Global Clinical Development
(Executive Vice President and CMO, Sunovion Pharmaceuticals Inc.)

4. New Challenge in Oncology Area: Making Meaningful Medicines

David J. Bearss, Ph.D.

CEO, Tolero Pharmaceuticals, Inc.

5. Q&As

Introduction

Masayo Tada
President and CEO

Towards Sustainable Growth

Hiroshi Noguchi, Ph.D.
Senior Executive Vice President and CSO

- ◆ **Aspire to be a globally active R&D-based company**
- ◆ **Contribute to medical care through leading-edge technologies**

R&D Basic Strategy

Early recovery from LATUDA Cliff: Focus on late-stage clinical studies

- **Be certain to obtain approval of late-stage development pipeline promptly**

For our future growth: Further activation in drug research

- **Discover first-in-class drugs or drugs with distinct characteristics**
 - Select and concentrate on focus therapeutic areas (Psychiatry & Neurology and Oncology), adopt business unit structure
 - Discover drugs by drawing upon our strengths
 - Ensure “POC First” principle and enhance translational research
 - Bring in cutting-edge technologies
 - Reinforce use of “outside” resources

R&D organizations & Personnel system

- **Management according to the development stage**
 - Early-stage: Venture approach, express abilities as an individual
 - Late-stage: Organizational power, cooperation
- **New personnel system (professional contributor: PC)**
 - Created PC1/PC2 positions based on individual expertise and achievements

Performance Image after the 3rd MTBP

Drop expected in FY2019 as LATUDA[®] loses its exclusivity in North America.
 Shooting for early recovery after FY2020 through launches and growth of late-stage products.

Net sales image
 (billions of yen)

Inorganic growth of late-stage products

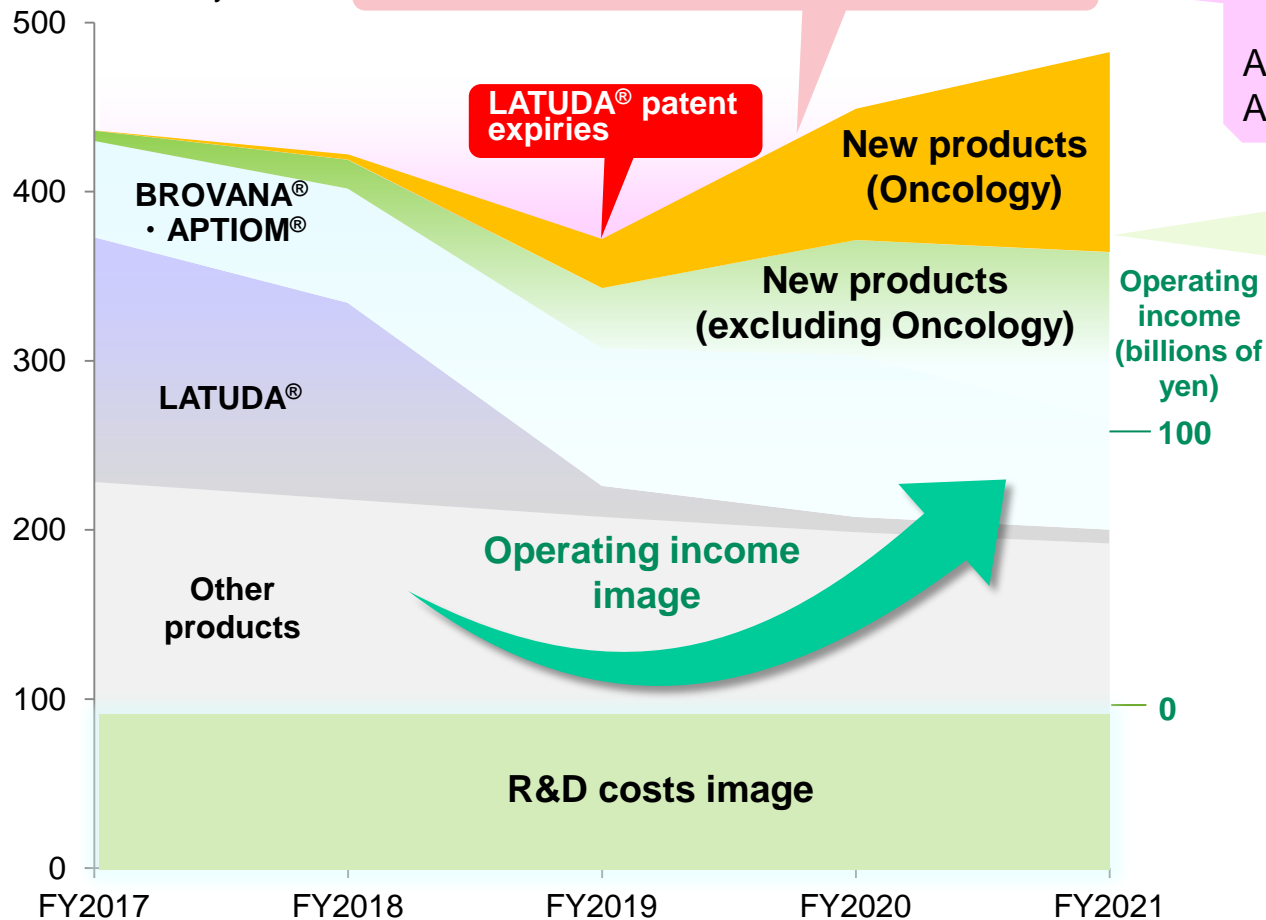
LATUDA[®] patent expires

Acquired after May 2016
 UTIBRON, SEEBRI, ARCAPTA (U.S.)
 Approved in U.S.
 APL-130277 (Global) Ph3 in U.S.
 Alvocidib (Global) Ph2 in U.S.

Main products for launch (planned)

Oncology area
 Napabucasin (Japan and U.S.)
 Amcasertib (Japan and U.S.)
 DSP-7888 (Japan and U.S.)

The other areas
 SUN-101 (U.S.)
 Dasotraline (U.S.)
 SB623 (U.S.)
 Lurasidone (Japan)
 DSP-1747 (Japan)



(Created in May 2016)

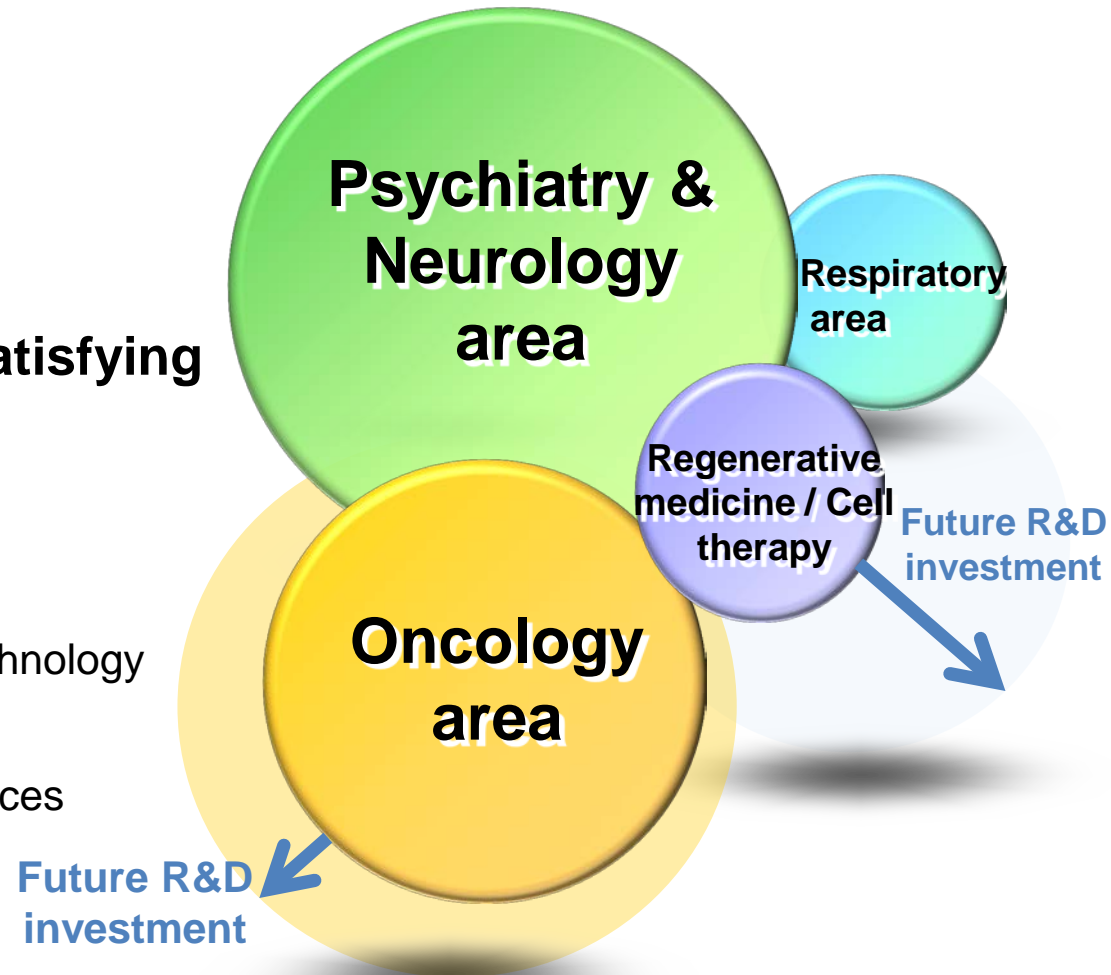
Key Late-stage Pipeline : Progress in FY2016

| Compounds | Progress | Submission target |
|---|--|--|
| Napabucasin | <ul style="list-style-type: none"> Gastric, Gastro-esophageal junction adenocarcinoma (combination): Completed recruitment for Phase 3 study Colorectal, Pancreatic cancer (combination): Started recruitment for Phase 3 studies CCTG announced results of CO.23 study (Colorectal / monotherapy): No significant difference was observed in OS between napabucasin and placebo, but napabucasin significantly improved OS in patients with high p-STAT3 expression. | FY2018 (Gastric, Gastro-esophageal junction adenocarcinoma) |
| Alvocidib | <ul style="list-style-type: none"> Acquired through Tolero in January 2017 Ongoing Phase 2 study for relapsed or refractory AML (combination / with biomarker) | FY2018 (at earliest) |
| Dasotraline | <ul style="list-style-type: none"> ADHD (pediatric and adult): Significant improvement in the primary endpoint was observed in pediatric Phase 2/3 study. No Significant improvement in the primary endpoint was observed in adult Phase 3 study BED: Significant improvement in the primary endpoint was observed in Phase 2/3 study | FY2017 (ADHD/ Pediatric and Adult) |
| Apomorphine Sublingual film (APL-130277) | <ul style="list-style-type: none"> Acquired through Cynapsus in October 2016 Ongoing Phase 3 study for OFF episodes associated with Parkinson's disease | FY2017 |
| Glycopyrronium bromide (SUN-101) | <ul style="list-style-type: none"> NDA for COPD accepted by the FDA in October 2016 (PDUFA date: May 29, 2017) | Filed |
| UTIBRON, SEEBRI, ARCAPTA | <ul style="list-style-type: none"> In December 2016, acquired exclusive rights from Novartis for commercialization rights in the US of three products for COPD | (Approved) |

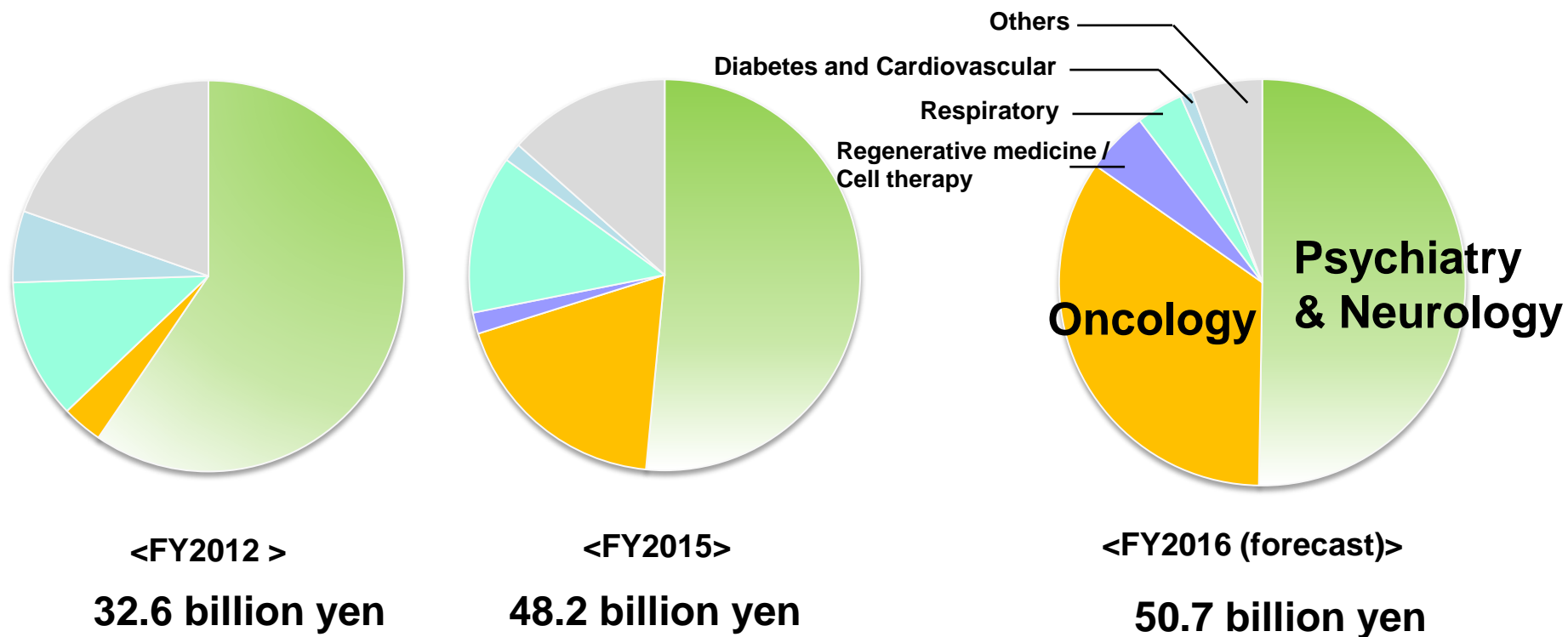
Current Focus Areas & Future R&D Investment Strategy

Prioritize

- Innovation
 - Competitive advantages
 - Marketability
 - Growth potential
- **Take on the challenge of satisfying unmet medical needs**
From “point“ to “plane“
 - **Time axis**
Addressing the needs of the time
Rapid advances in Science & Technology
 - **Own strengths**
Past accomplishments & experiences
 - **Toward the future**
Growth areas

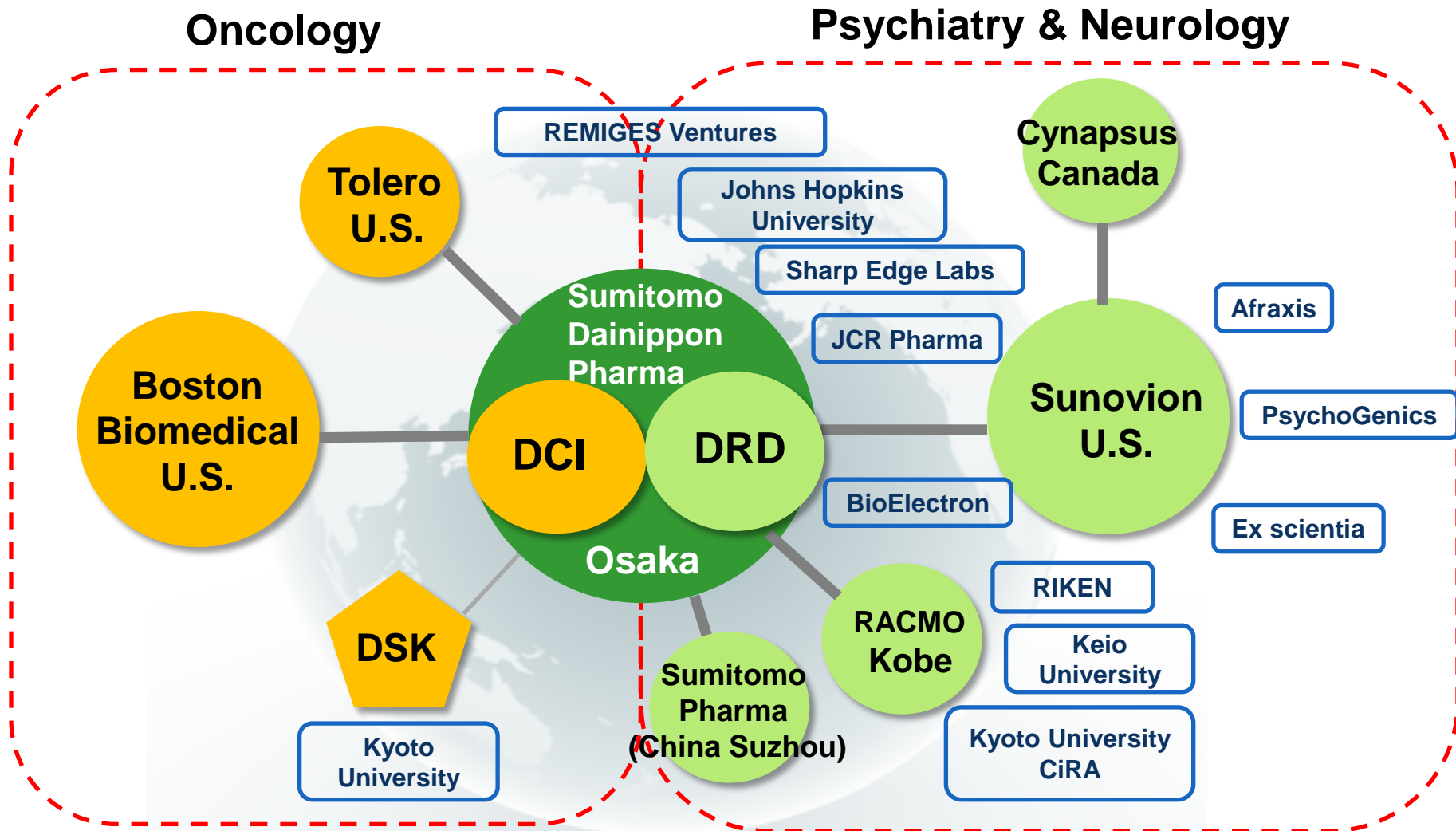


Trends in R&D Costs (direct) & Allocation to Areas



Focus investment on
Psychiatry & Neurology (including regenerative medicine / cell therapy)
Oncology

Hub & Spoke, Central & Satellite System



DCI: DSP Cancer Institute

DSK: Kyoto University and Sumitomo Dainippon Pharma Joint Research Project

DRD: Drug Research Division

RACMO: Regenerative & Cellular Medicine Office

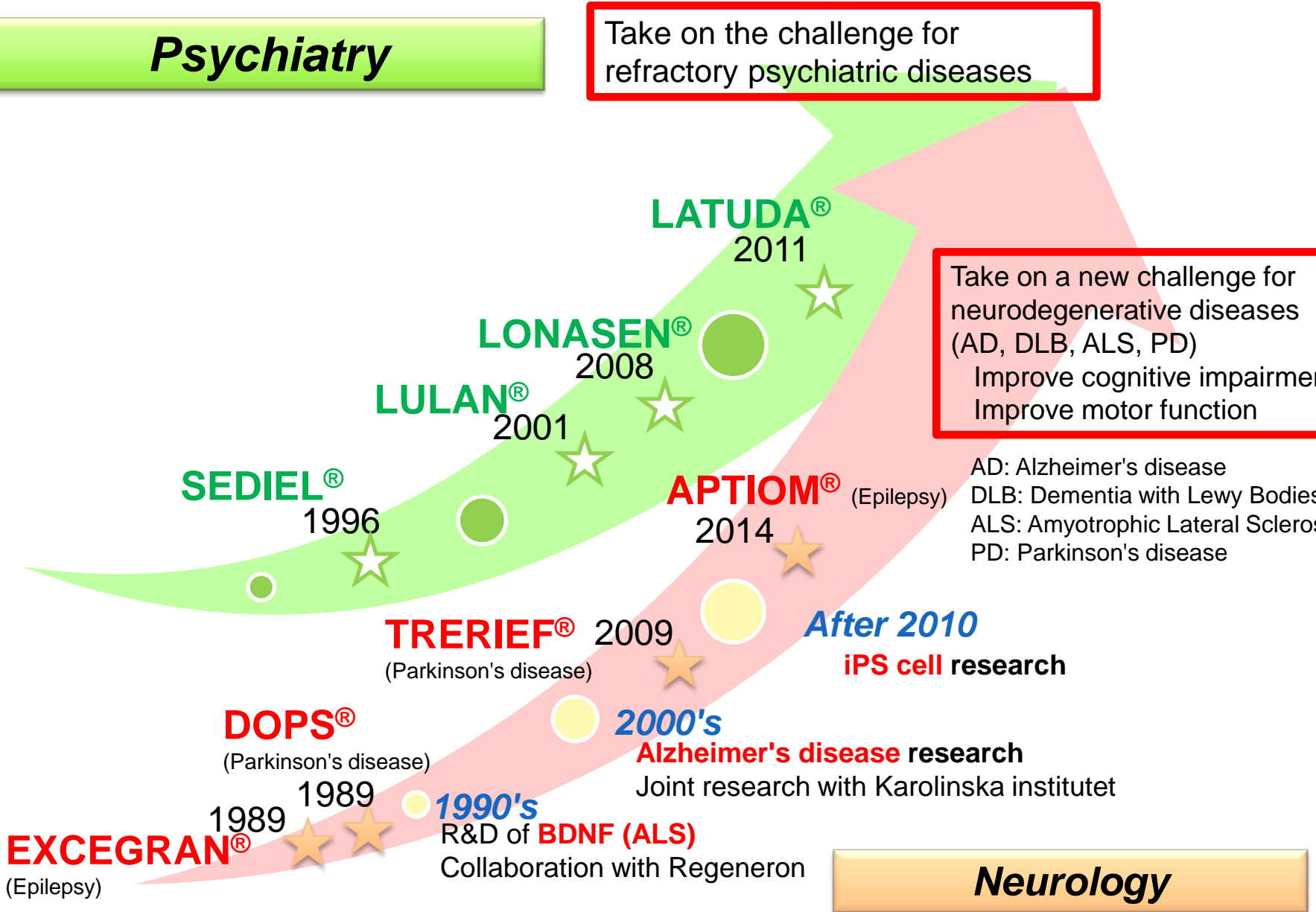
Expansion from Psychiatry to Neurology

Psychiatry

Take on the challenge for refractory psychiatric diseases

Take on a new challenge for neurodegenerative diseases (AD, DLB, ALS, PD)
Improve cognitive impairment
Improve motor function

AD: Alzheimer's disease
DLB: Dementia with Lewy Bodies
ALS: Amyotrophic Lateral Sclerosis
PD: Parkinson's disease



Psychiatry

Take on the challenge for refractory psychiatric diseases

Take on a new challenge for neurodegenerative diseases (AD, DLB, ALS, PD)
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SEDIEL®
1996

LULAN®
2001

LONASEN®
2008

LATUDA®
2011

APTIOM® (Epilepsy)
2014

TRERIEF® 2009
(Parkinson's disease)

DOPS®
(Parkinson's disease)
1989

2000's
Alzheimer's disease research
Joint research with Karolinska institutet

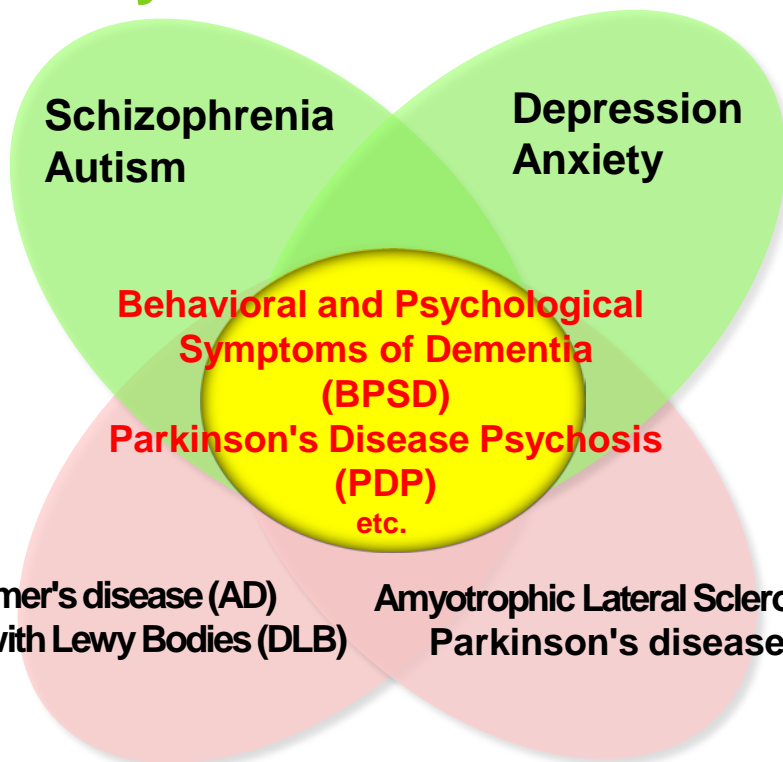
After 2010
iPS cell research

EXCEGRAN® (Epilepsy)
1989
1990's
R&D of **BDNF (ALS)**
Collaboration with Regeneron

Neurology

R&D Strategy: Fusion of Psychiatry & Neurology

Psychiatry



Neurology

◆ New indications for psychiatric drugs

Expansion to associated or peripheral symptoms in neurodegenerative disease

BPSD

PDP

◆ Expand to new indications from the originally specified disease

From Orphan diseases to

Common (segmented) diseases

◆ Unique approach

Phenotypic drug discovery (animal and cell)

Biomarkers (EEG, fMRI, PET)

Non-human primates

EEG: electroencephalogram

fMRI: functional nuclear magnetic resonance imaging

PET: positron emission tomography

Continual R&D Pipeline

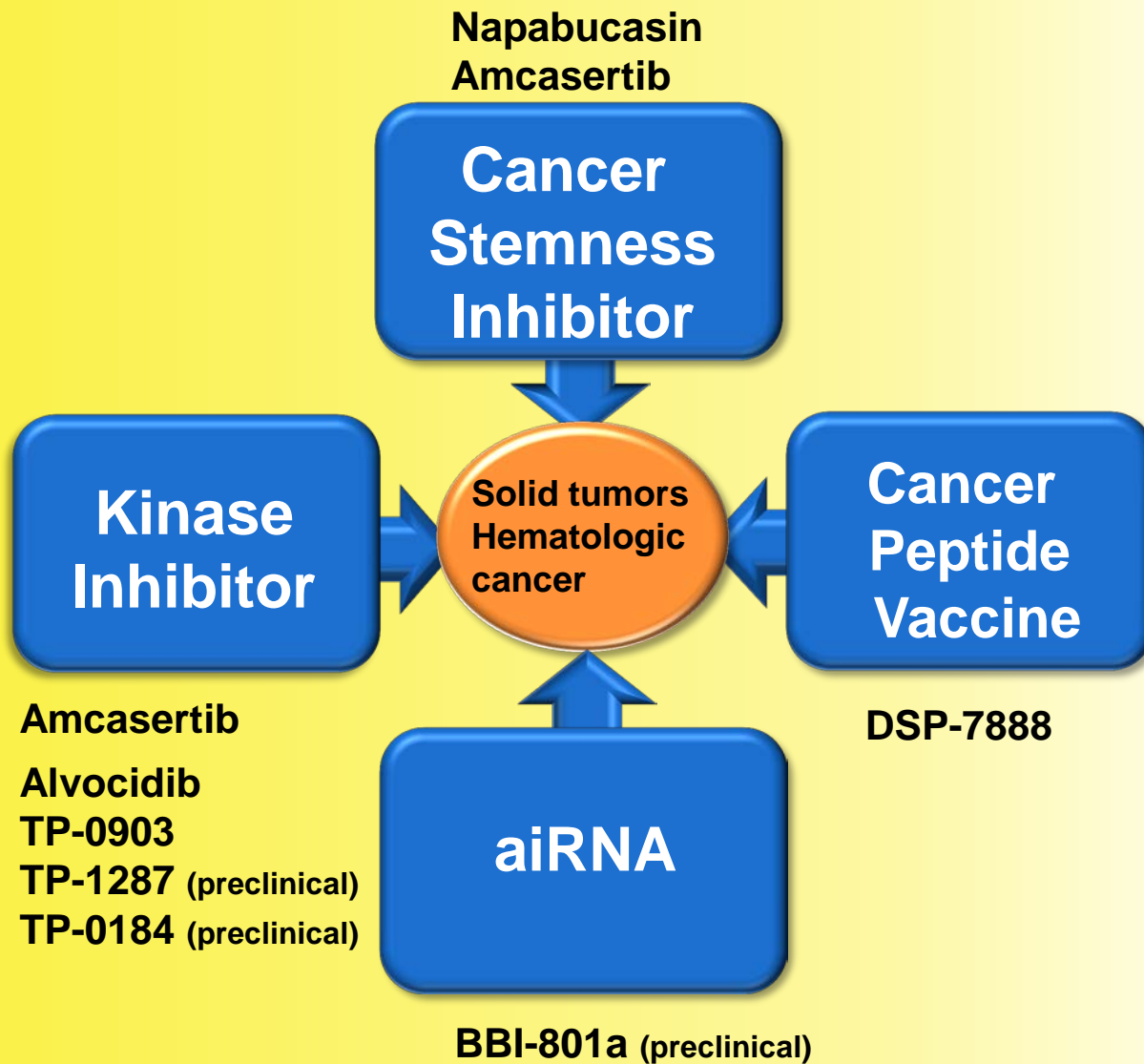
| Area | Discovery/PC | Phase 1 | Phase 2 | Phase 3 |
|--|---|---|--|--|
| Psychiatry | Early program (Neurotransmitter Monoamine system) | DSP-1200 Treatment-resistant depression | SEP-363856 PD psychosis, Schizophrenia | dasotraline ADHD, BED |
| | | DSP-3748 CIAS | | |
| | | DSP-6745 PD psychosis | | |
| Neurology | Early program (Core & Peripheral symptom Reduction neurodegenerative progress) | DSP-2230 Neuropathic pain | EPI589 PD, ALS | TRERIEF® Parkinsonism in DLB |
| | | | | APL-130277 OFF episodes associated with PD |
| (Regenerative medicine / Cell therapy) | Early program (iPSC-RPE, iPSC-dopamine neuron, etc.) | | SB623 Chronic stroke | |

CIAS: Cognitive Impairments Associated
with Schizophrenia
RPE: Retinal Pigment Epithelium

PD: Parkinson's Disease
ALS: Amyotrophic Lateral Sclerosis

ADHD: Attention Deficit Hyperactivity Disorder
BED: Binge Eating Disorder
DLB: Dementia with Lewy Bodies

R&D strategy: Oncology

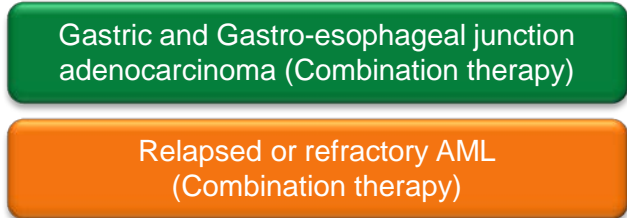


- ◆ Meet the needs of the times
- ◆ Take on the challenge of adopting innovative concepts and technology
- ◆ Fuse external knowledge, skills and culture with ours (Boston Biomedical, Tolero, Academia)

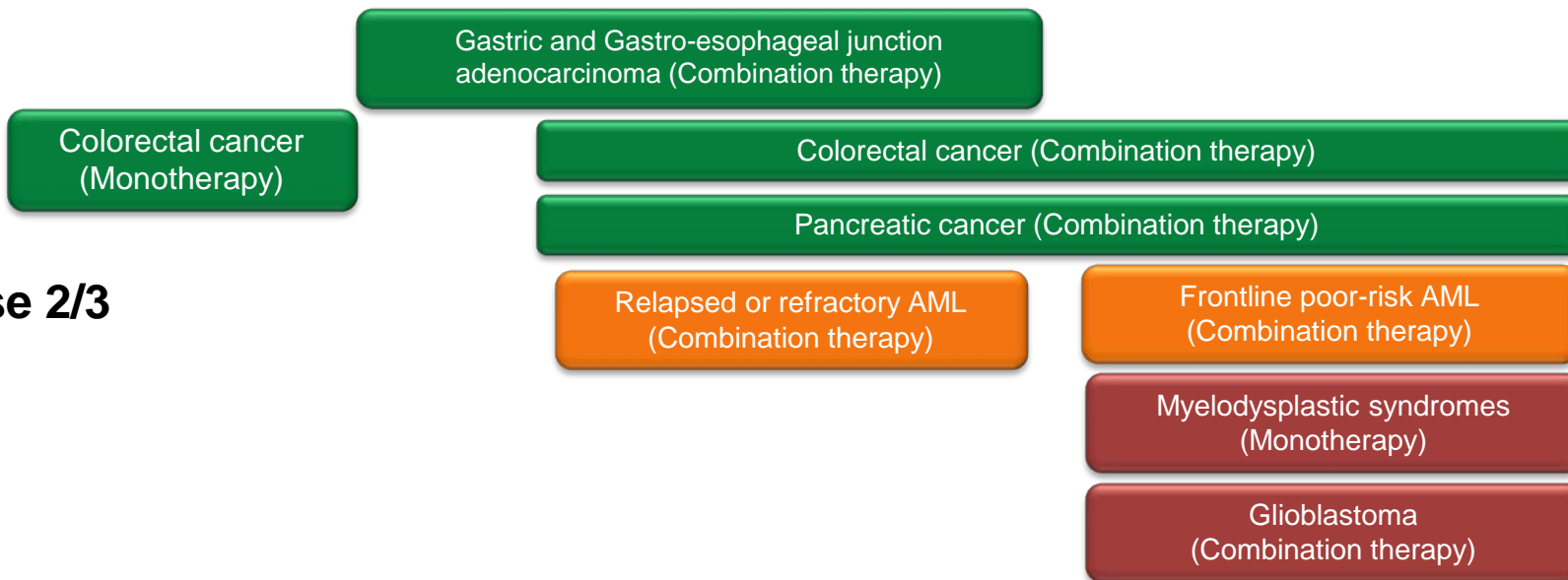
Aim to Continual Approval & Launch



Launch



Phase 2/3



Napabucasin Clinical Development Status

● Cancer Stemness Inhibitor Napabucasin: Key late-stage clinical studies

- ✓ Gastric and Gastro-esophageal junction adenocarcinoma (combination): Phase 3 study ongoing, Completed LPI, Submission target FY2018
- ✓ Colorectal cancer (combination): Phase 3 study ongoing
- ✓ Pancreatic cancer (combination): Phase 3 study ongoing

● Results of Phase 1b/2 study (BBI608-246) in colorectal cancer combination therapy with FOLFIRI, or FOLFIRI and bevacizumab (open label)

➤ Study Results :

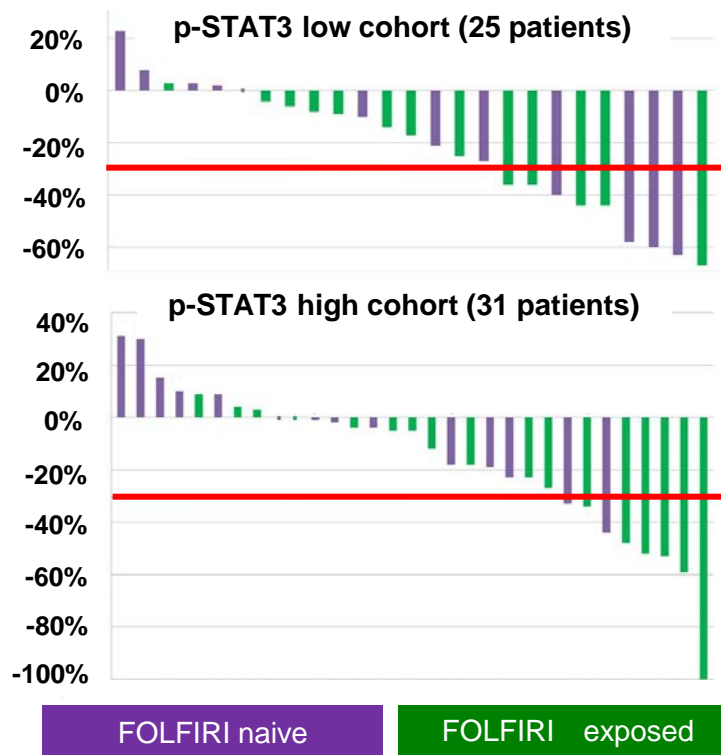
- ✓ Napabucasin showed signs of anti-cancer activity regardless of FOLFIRI-pretreatment or p-STAT3 status

(56 evaluable patients)

| Subset | Disease control rate (DCR) | Overall response rate (ORR) |
|------------------|----------------------------|--|
| Evaluable 56 pts | 88% (49/56 pts) | 29% (16/56 pts) (1 pt achieving CR) |
| FOLFIRI naïve | 93% (28/30 pts) | 33% (10/30 pts) |
| FOLFIRI exposed | 81% (21/26 pts) | 23% (6/26 pts) |
| p-STAT3 low | 92% (23/25 pts) | 32% (8/25 pts) |
| p-STAT3 high | 84% (26/31 pts) | 26% (8/31 pts) |

- LPI: Last Patient-in
- FOLFIRI (Combination with fluorouracil, leucovorin, irinotecan)

Percentage Change in target lesions (Best response)



Cancer Peptide Vaccine (DSP-7888)

- **Characteristic:** The peptide inducing WT1-specific CTL + peptide inducing helper T cells
Targeted disease: Solid tumors (Pediatric brain tumor), Hematologic malignancies (Myelodysplastic syndromes (MDS))

WT1: Wilms' tumor gene 1

CTL : Cytotoxic T Lymphocyte

- **Phase 1 study for MDS**

➤ **Study Results :**

- ✓ Disease Control Rate was 66.7% in evaluable 12 patients

Overall Survival in azacitidine failure higher-risk MDS patients

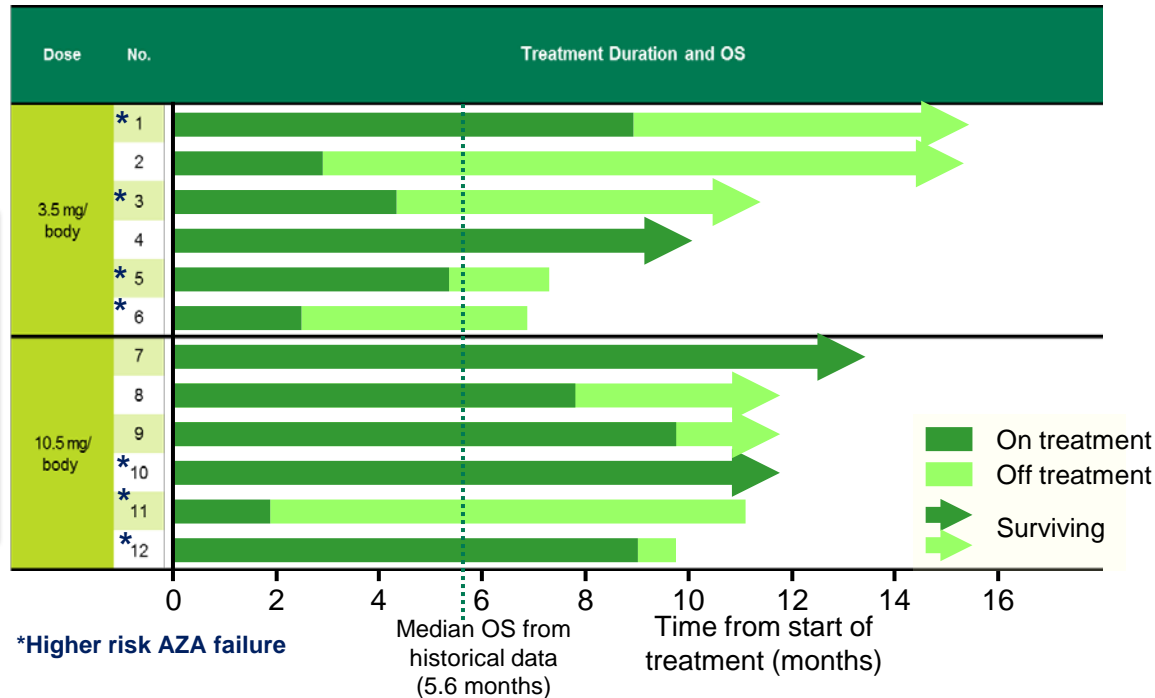
DSP-7888 (7 patients):
6.8 to 15.5 month¹⁾

Historical data (435 patients):
Median 5.6 months²⁾

➤ **Future plans:**

- ✓ Phase 2/3 study will be initiated in FY 2017

Clinical Responses and Survival Outcomes of Individual Patients



1) Miyakoshi S et. al. ASH 2016(Abtract 4335)

2) Prebet T et. al. *J Clin Oncol* 2011;29:3322-7

Tolero's Pipeline & Discovery Capabilities

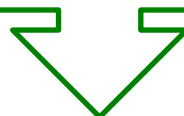
➤ Tolero's pipeline

| Development code | Generic name | Mechanism of action | Target indication | Development location | Development stage |
|------------------|--------------|--|---|----------------------|------------------------|
| - | Alvocidib | CDK9 inhibitor | Acute myeloid leukemia | U.S. | Phase 2 (Completed) |
| | | | Acute myeloid leukemia (Biomarker) | U.S. | Phase 2 |
| | | | Myelodysplastic syndromes | U.S. | Preclinical |
| TP-0903 | TBD | AXL receptor tyrosine kinase inhibitor | Solid tumors, Hematologic malignancies | U.S. | Phase 1 |
| TP-1287 | TBD | CDK9 inhibitor | TBD | U.S. | Preclinical |
| TP-0184 | TBD | ALK2/BMPR Signaling Inhibitor | TBD | U.S. | Preclinical |

* In addition to the above list, Tolero possesses two compounds in the preclinical stage

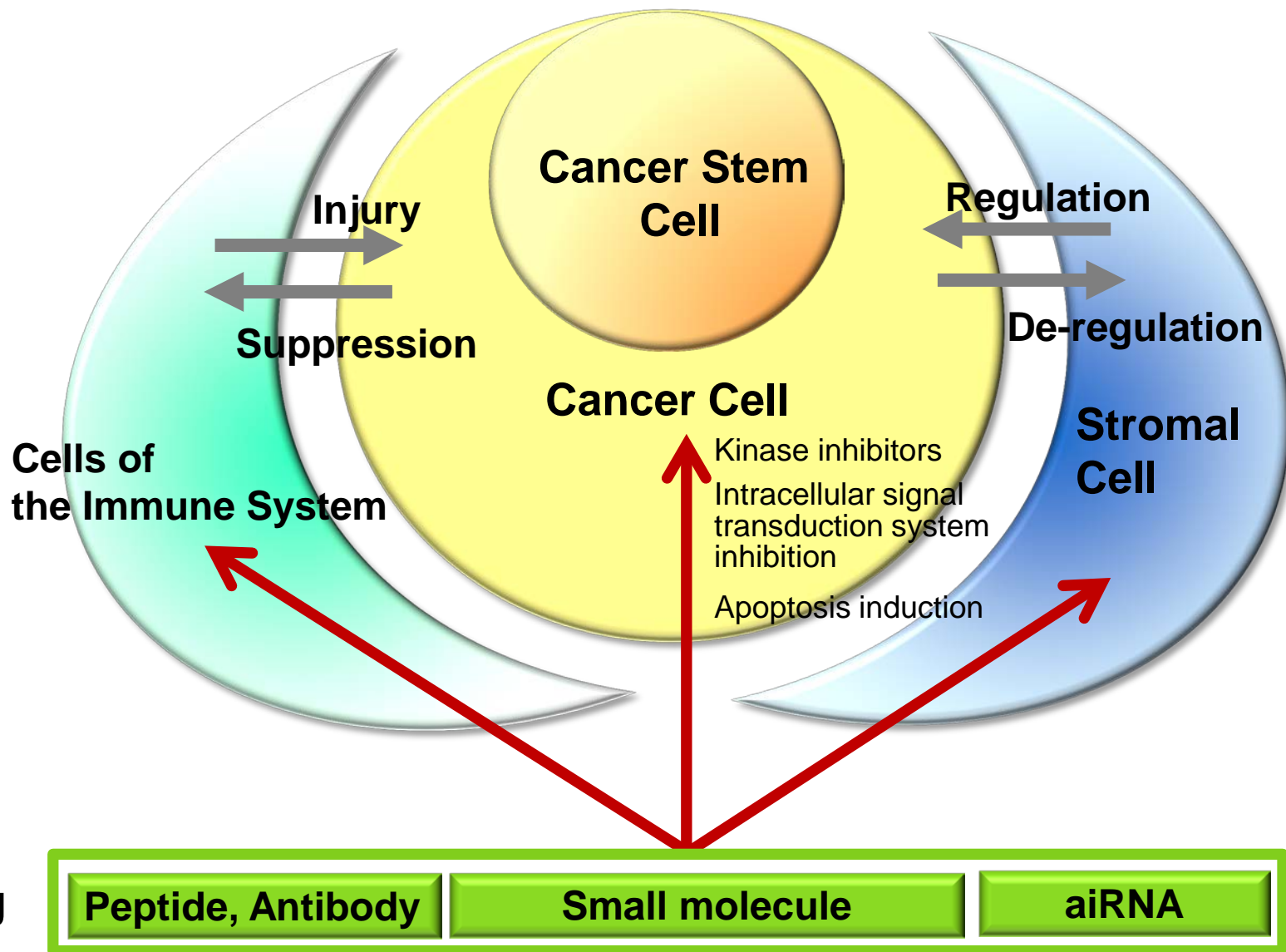
➤ Tolero's drug discovery capabilities

- Experienced personnel who have been involved in drug discovery and clinical development targeting kinases for more than 10 years
- Unique evaluation system that assesses disease relevance and in-silico platform to discover disease-related kinases



Select target indication, such as hematologic malignancies, most relevant to targeted kinase

Cancer Drug Research: Outlook for the Future



Towards the Future

- **Make achievements with limited R&D resources**
 - ✓ Selection and Concentration
 - ✓ Advancing the R&D system, Securing investment in early-stage programs
- **Continuously develop and reinforce our own science and technology platform (strength)**
 - ✓ In silico drug discovery, Disease iPS, Brain targeted DDS
 - ✓ Phenotypic screening system, Non-human primate system
- **Accelerate use of external resources**
 - ✓ Secure “drug seeds” through open innovation
 - ✓ Out-license of early assets
 - ✓ Cost sharing with partners through joint research or collaboration

Aspire to be a globally active R&D-based company, through leading-edge science and technologies

Ensure sustainable growth through the creation of new value

Psychiatry & Neurology and Respiratory Areas: Pipeline Driving Sustainable Growth

Dasotraline

**Apomorphine
Sublingual film
(APL-130277)**

**Glycopyrronium
bromide
(SUN-101)**



Antony Loebel, M.D

Executive Officer, Head of Global
Clinical Development

Executive Vice President and CMO,
Sunovion Pharmaceuticals Inc.

New Challenge in Oncology Area: Making Meaningful Medicines

Alvocidib



David J. Bearss, Ph.D

Chief Executive Officer
Tolero Pharmaceuticals, Inc.

Psychiatry & Neurology Area, Respiratory Area: Pipeline Driving Sustainable Growth

Antony Loebel, M.D.
Executive Officer, Head of Global Clinical Development
Executive Vice President and CMO, Sunovion Pharmaceuticals Inc.

Today's Agenda



GCD OVERVIEW



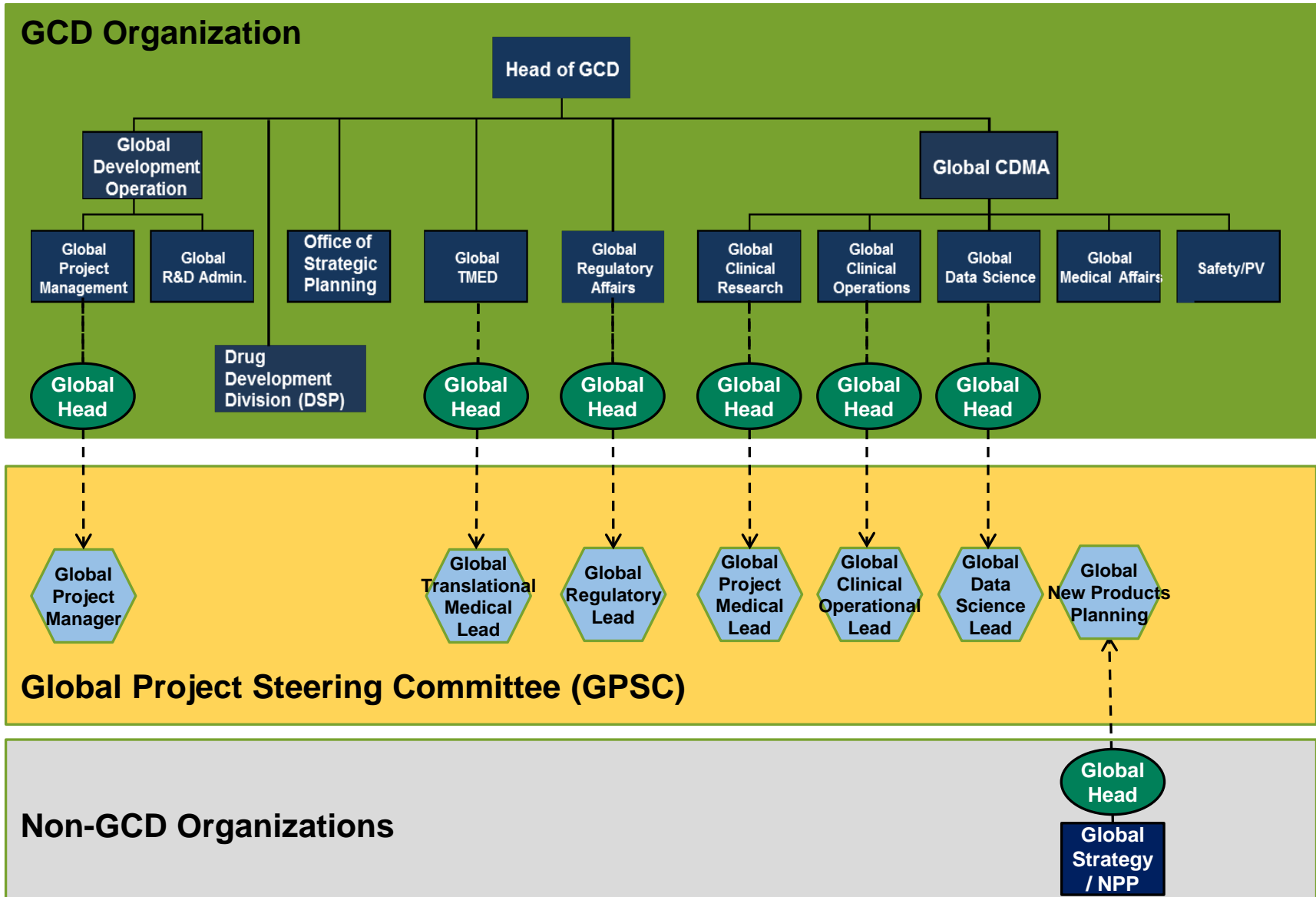
PSYCHIATRY FRANCHISE



NEUROLOGY FRANCHISE



RESPIRATORY FRANCHISE



Focus on One Team, Values, and Goals





Our Pipeline (as of January 27, 2017)

● Topics

| Brand name/ Product code | Generic name | Proposed indication | Development location | Phase 1 | Phase 2 | Phase 3 | Submitted |
|-----------------------------|--------------------------------------|---|----------------------|---------|---------|---------|-----------|
| LATUDA® | lurasidone hydrochloride | Schizophrenia | China | | | | |
| | | Schizophrenia | Japan | | | | |
| | | Bipolar I depression, Bipolar maintenance | Japan | | | | |
| | | Pediatric, adolescent Bipolar I disorder (new indication) | U.S. | | | | |
| SEP-225289 | dasotraline | Adult attention-deficit hyperactivity disorder (ADHD) | U.S. | | | | |
| | | Pediatric attention-deficit hyperactivity disorder (ADHD) | U.S. | | | | ※ Ph 2/3 |
| | | Binge eating disorder (BED) | U.S. | | | | ※ Ph 2/3 |
| SEP-363856 | TBD | Schizophrenia, Parkinson's disease psychosis | U.S. | | | | |
| | | Schizophrenia | Japan | | | | |
| APTIOM® | eslicarbazepine acetate | Partial-onset seizures in children (4yr+) – adjunctive and monotherapy (new indication) | U.S. | | | | |
| APL-130277 | apomorphine hydrochloride Sublingual | OFF episodes associated with Parkinson's disease | U.S. | | | | |
| SB623 | TBD | Chronic Stroke | U.S. | | | | |
| SUN-101/eFlow® | glycopyrronium bromide | Chronic obstructive pulmonary disease (COPD) | U.S. | | | | |

● Other pipeline

| | | |
|----------|------------------|--|
| LONASEN® | blonanserin | Schizophrenia (Submitted/China), (Pediatric usage) Schizophrenia (Ph3/Japan), (New formulation: Transdermal patch) Schizophrenia (Ph3/Japan) |
| TRERIEF® | zonisamide | (New indication) Parkinsonism in Dementia with Lewy Bodies (DLB) (Ph3/Japan) |
| EPI-743 | vatiquinone | Leigh syndrome (Ph2/3 completed/Japan) |
| EPI-589 | TBD | Parkinson's disease (Ph2/US), Amyotrophic lateral sclerosis (ALS) (Ph2/US) |
| DSP-1747 | obeticholic acid | Nonalcoholic steatohepatitis (NASH) (Ph2/Japan) |
| DSP-6952 | TBD | IBS with constipation, Chronic idiopathic constipation (Ph2/Japan) |
| DSP-2230 | TBD | Neuropathic pain (Ph1) |
| DSP-3748 | TBD | Cognitive Impairment Associated with Schizophrenia (Ph1) |
| DSP-1200 | TBD | Treatment-resistant depression (Ph1) |
| DSP-6745 | TBD | Parkinson's disease psychosis (Ph1) |

**PSYCHIATRY FRANCHISE
FOCUSED ON
DIFFERENTIATED
THERAPIES FOR UNMET
NEEDS**



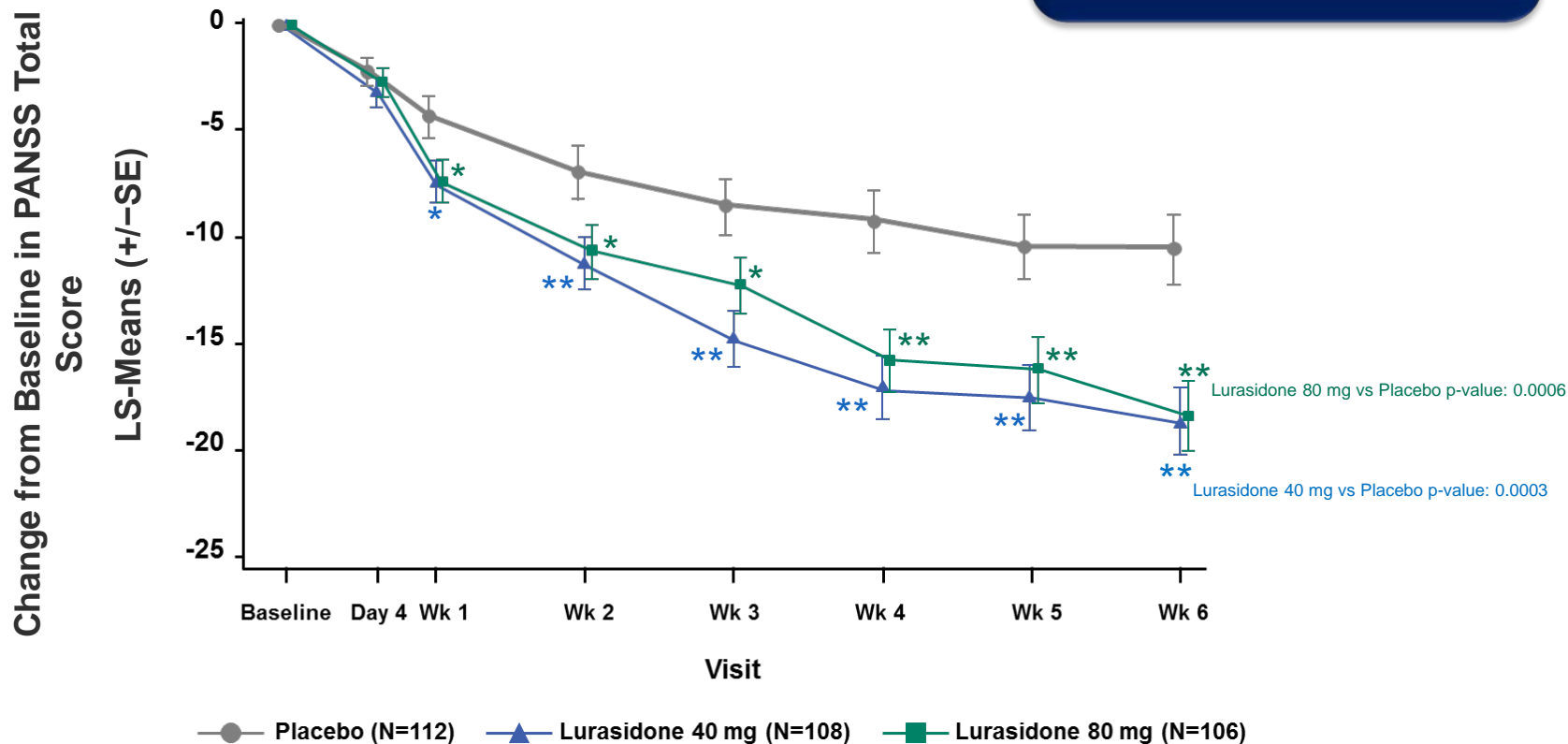
LATUDA for Adolescents with Schizophrenia



Study Design (Study 301)

- Six-week, randomized, double-blind, placebo-controlled, parallel-group, fixed dose study (LATUDA 40 or 80 mg/day)
- Adolescents (ages 13-17 years) with schizophrenia

LATUDA now approved by FDA for treatment of adolescents with schizophrenia



● Placebo (N=112) ▲ Lurasidone 40 mg (N=108) ■ Lurasidone 80 mg (N=106)

| | | | |
|---|------|------|------|
| BL Mean | 92.8 | 94.5 | 94.0 |
| Effect Size at Week 6 LOCF (vs. Placebo) | | 0.51 | 0.48 |

*P<0.05; **P<0.01



LATUDA for Children & Adolescents with Bipolar Depression

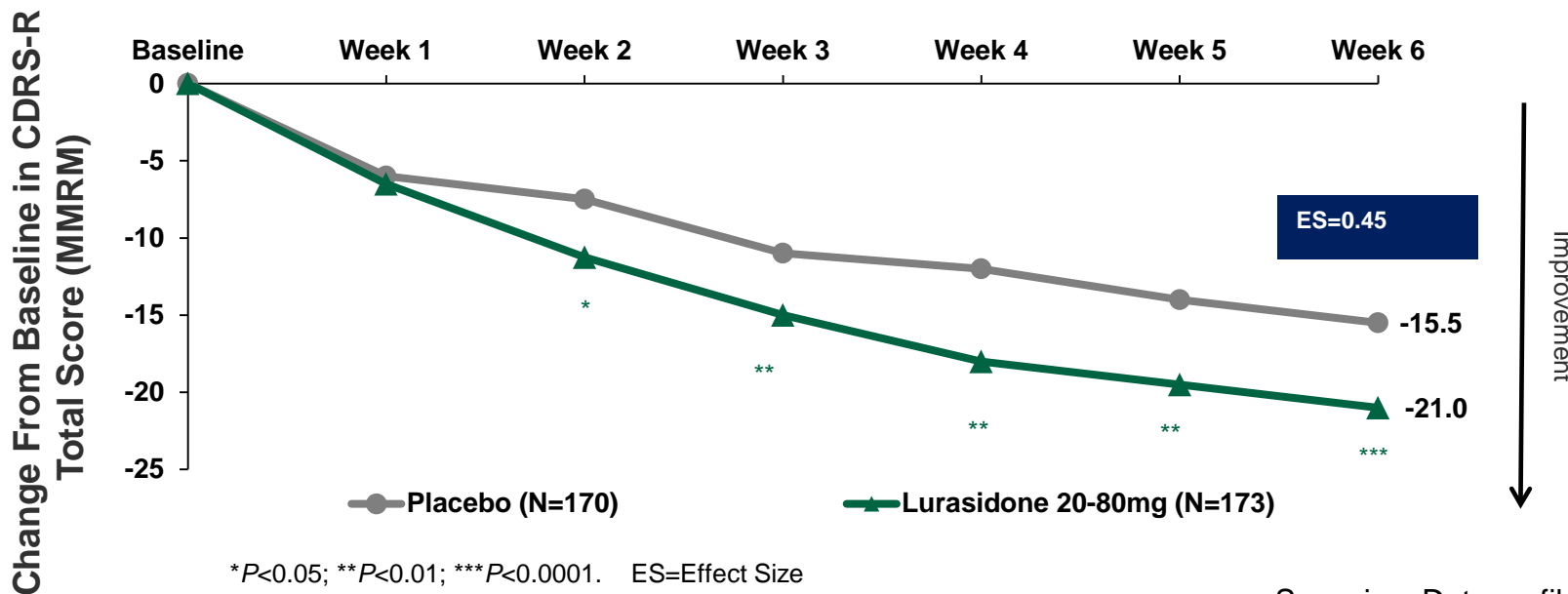
Study Design (Study 326)

- Six-week, randomized, double-blind, placebo-controlled, parallel-group, flexible dose study (LATUDA 20-80 mg/day)
- Children and adolescents (ages 10-17) with bipolar I disorder

Results

- Demonstrated statistically significant and clinically meaningful improvement versus placebo on primary and secondary endpoints
- LATUDA was generally well-tolerated with minimal effects on weight and metabolic parameters

Primary Efficacy Endpoint: Children Depression Rating Scale – Revised (CDRS-R) Total Score





Dasotraline (SEP-225289)



Attention-deficit hyperactivity disorder (ADHD)
Binge eating disorder (BED)



Attention Deficit Hyperactivity Disorder (ADHD)

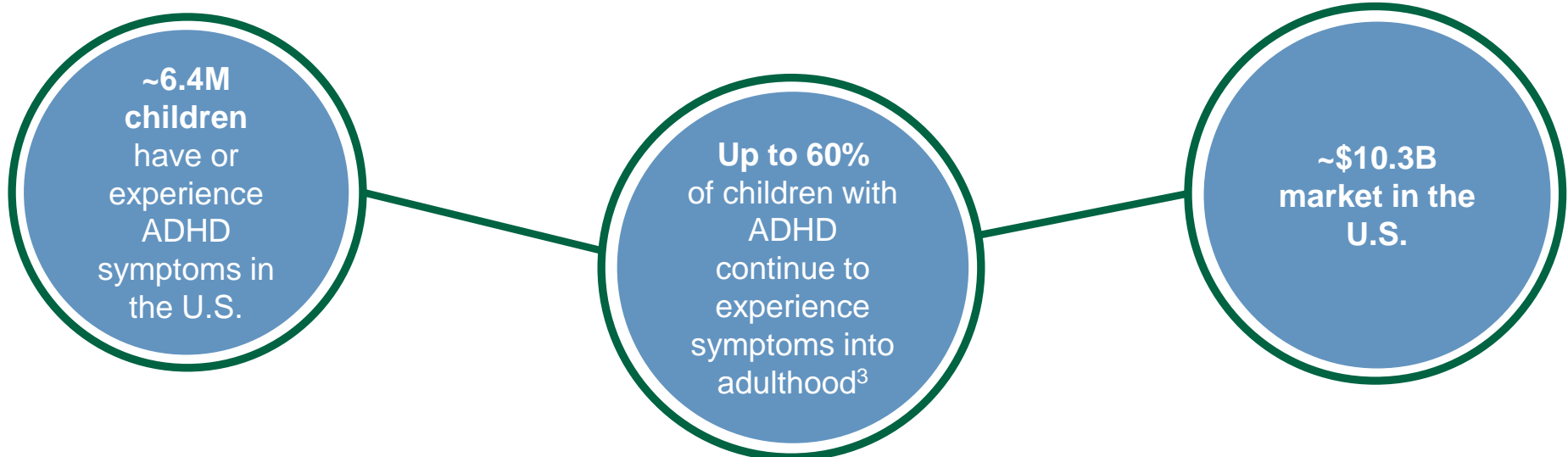
ADHD is a persistent pattern of *inattention and/or hyperactivity-impulsivity* that interferes with functioning and development.¹

CHILDREN

Children with ADHD have poorer *social relationships* and more frequent and severe *injuries* than peers without ADHD.²

ADULTS

Symptoms impact *social and occupational functioning*, leading to high levels of unemployment, workplace impairment and reduced productivity.^{4, 5, 6}



¹ American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders.

² Centers for Disease Control and Prevention. Data and Statistics.

³ Innov Clin Neurosci. Our Current Understanding of Adult ADHD.

⁴ Prim Care Companion J Clin Psychiatry. Assessing Adults With ADHD and Comorbidities.

⁵ International Archives of Occupational and Environmental Health. The negative impact of attention-deficit/hyperactivity disorder on occupational health in adults and adolescents.

⁶ WebMD. Attention Deficit Hyperactivity Disorder: ADHD in Adults.



Dasotraline is a long-lasting dopamine norepinephrine reuptake inhibitor (DNRI) with:

- Long duration of effect (t_{max} 10-12 hrs; t_{1/2} 47-77 hrs)
- Steady state achieved by 2 weeks
- Absence of wearing off and smoothness of effect
- Once-daily dosing
- Lower risk of abuse/diversion

In development for the following indications:

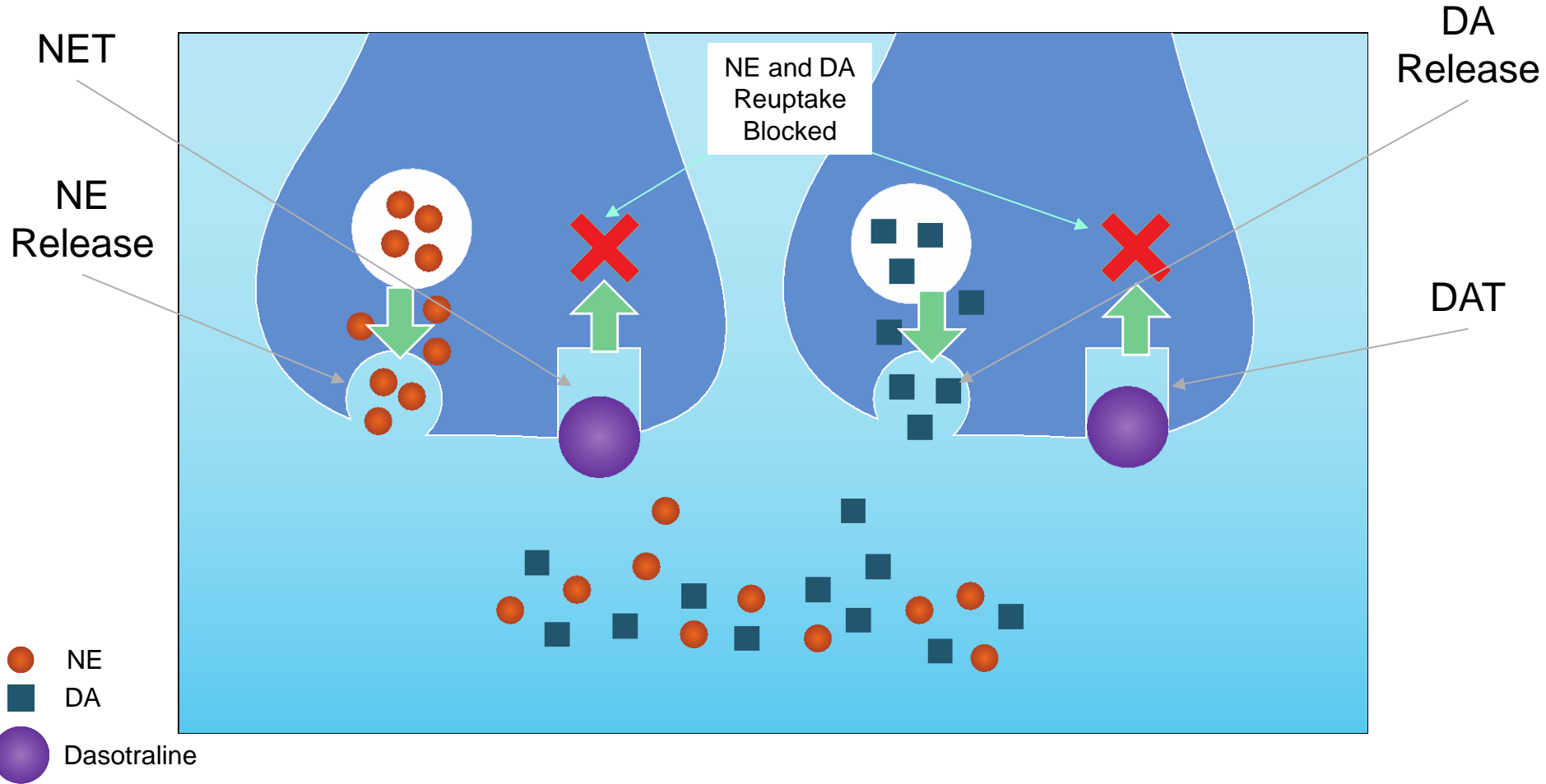
- Attention deficit hyperactivity disorder (ADHD)
- Binge eating disorder (BED)

Dasotraline could offer an alternative treatment option for ADHD and BED

- Stimulants
 - Are most commonly prescribed therapeutic agents for ADHD
 - Are highly effective but there is a growing problem of abuse
 - Do not provide continuous 24 hour coverage of ADHD symptoms
- Non-stimulants
 - Are not associated with abuse potential
 - Are perceived to be less effective



Dasotraline: Mechanism of Action



NE = Norepinephrine
DA = Dopamine
NET = NE Transporter
DAT = DA Transporter



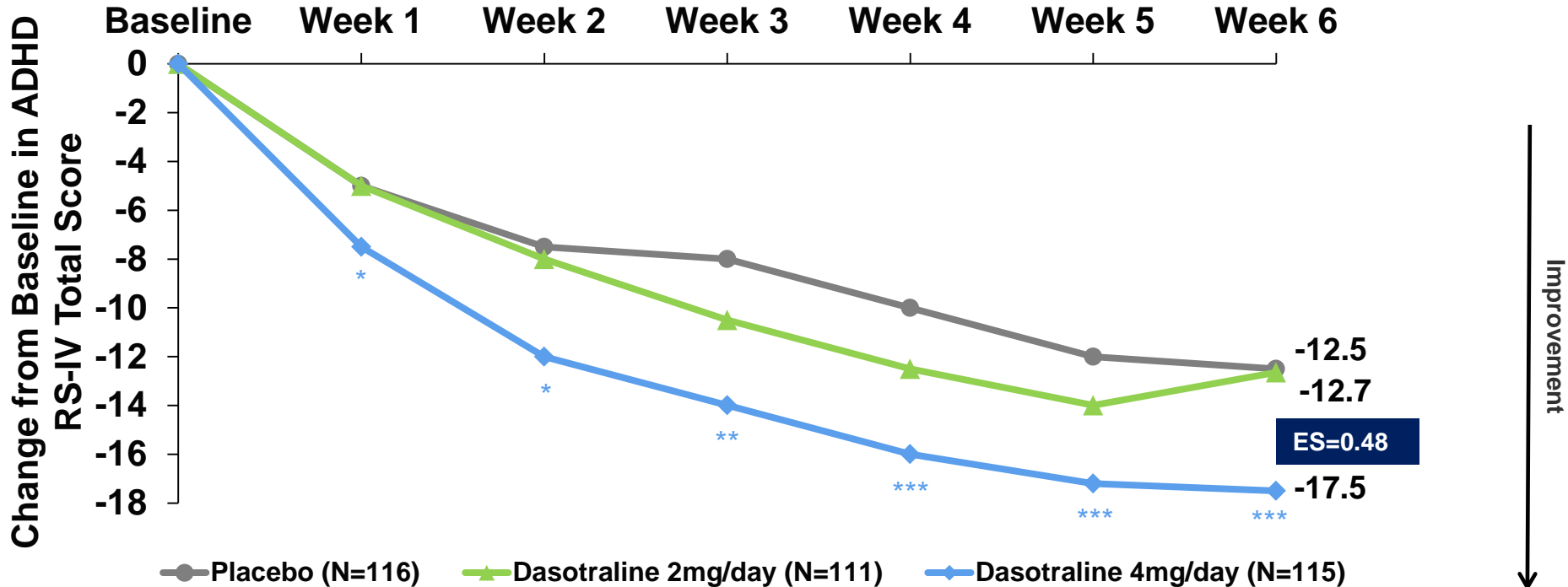
Dasotraline Efficacious in Children with ADHD

Study Design (SEP360-202)

- Six-week, double-blind, multi-center, placebo-controlled, parallel-group, fixed dose safety and efficacy trial in children ages 6-12 years

Results

- Study showed that the 4mg/per day dose demonstrated a statistically significant and clinically relevant difference compared to placebo (2mg/per day dose was not statistically significant)
- Dasotraline was generally well-tolerated



P values adjusted at week 6.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.0001$ ES=Effect Size



Dasotraline Efficacious in Adults with ADHD

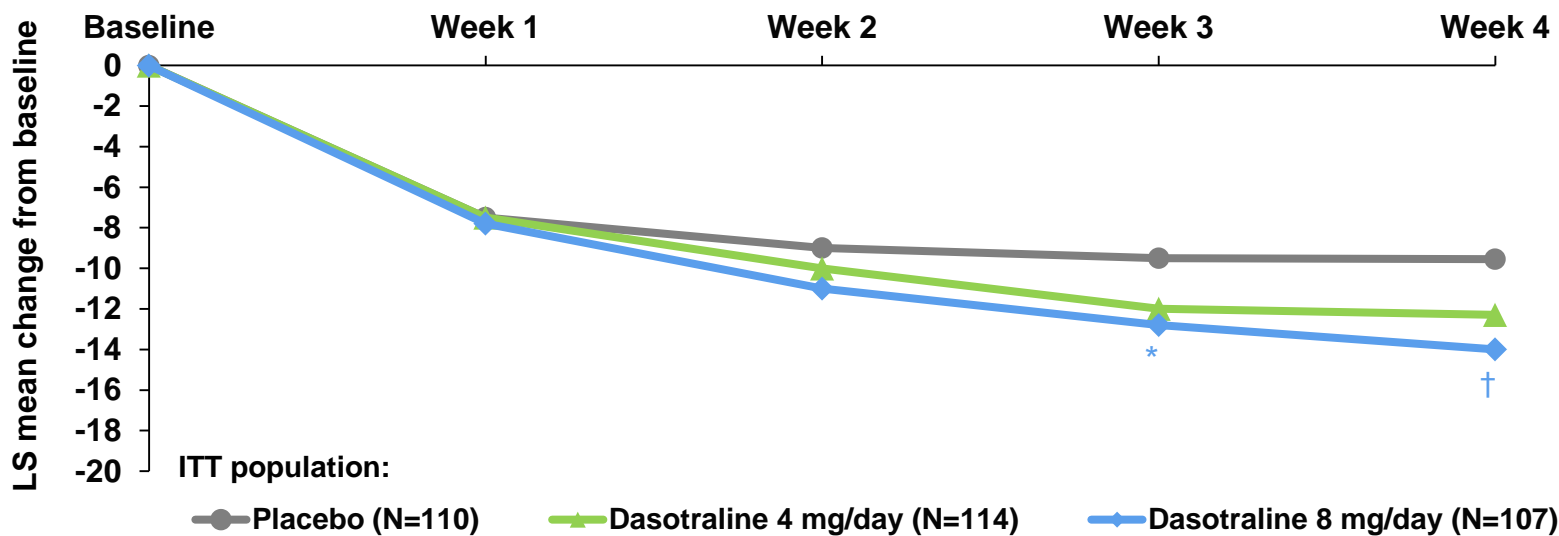
Study Design (SEP360-201)

- Four-week, randomized, double-blind, parallel-group, multi-center, placebo-controlled, fixed dose safety and efficacy trial in adults

Results

- Dasotraline 8 mg/day demonstrated statistically significant improvement compared to placebo on the primary efficacy endpoint
- Both dasotraline 4mg/per day and 8 mg/per day demonstrated a statistically significant and clinically relevant difference compared to placebo on the secondary endpoint
- Dasotraline was generally well-tolerated

ADHD RS-IV Total Score (MMRM) – Primary Endpoint LS Mean Change From Baseline



| | | | |
|----------|------|------|------|
| BL mean: | 36.7 | 36.8 | 36.6 |
|----------|------|------|------|

* $P < 0.05$

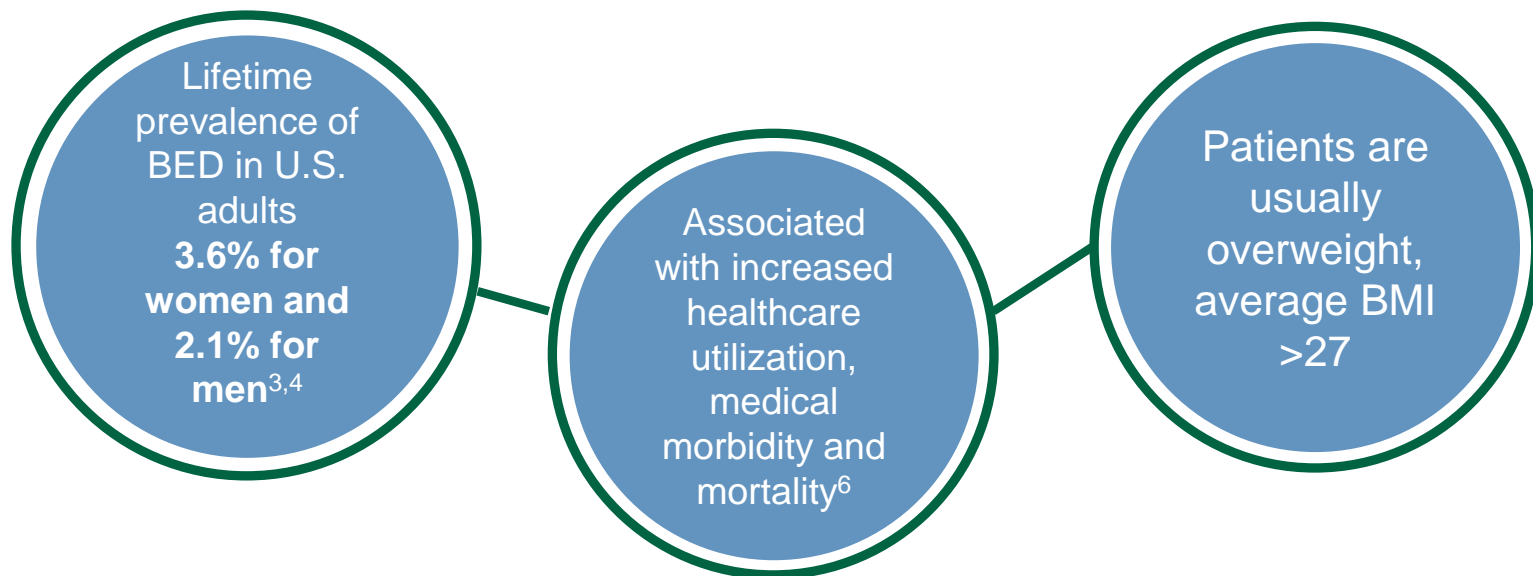
† $P < 0.025$

ADHD RS-IV, ADHD Rating Scale Version IV; BL, baseline; ITT, intent-to-treat; LS, least squares; MMRM, mixed-effects model for repeated measures



Binge-Eating Disorder (BED)

BED is an eating disorder that is characterized by recurrent episodes of binge eating that occur **at least once per week for three months** and can lead to a number of psychological and physical problems. Binge eating involves two key features: **eating a very large amount of food within a relatively short period of time** (e.g. within two hours) and feeling **a sense of loss of control while eating** (e.g. feeling unable to stop yourself from eating).^{1,2}



¹ American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders.

² Mayo Clinic. Binge-Eating Disorder.

³ Biological Psychiatry. The Prevalence and Correlates of Eating Disorders in the National Comorbidity Survey Replication.

⁴ Current Psychiatry Reports. Epidemiology of Eating Disorders: Incidence, Prevalence and Mortality Rates.

⁵ American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders.

⁶ American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders.



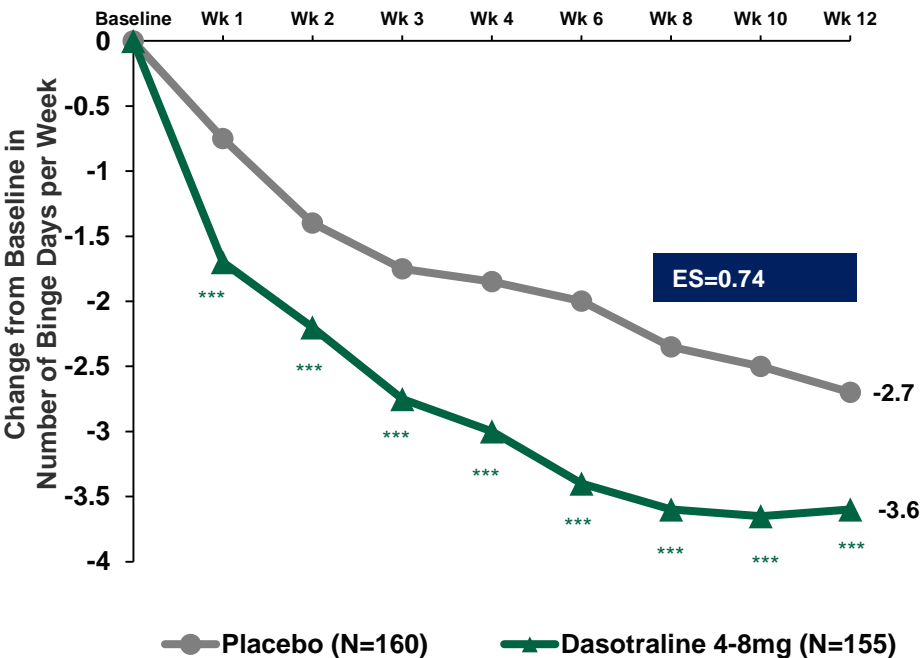
Dasotraline Demonstrates Efficacy in BED

Study Design (SEP360-221)

- Twelve-week, randomized, double-blind, parallel-group, multi-center, placebo-controlled, parallel-group, flexible-dose in adults with moderate to severe BED

Primary Endpoint

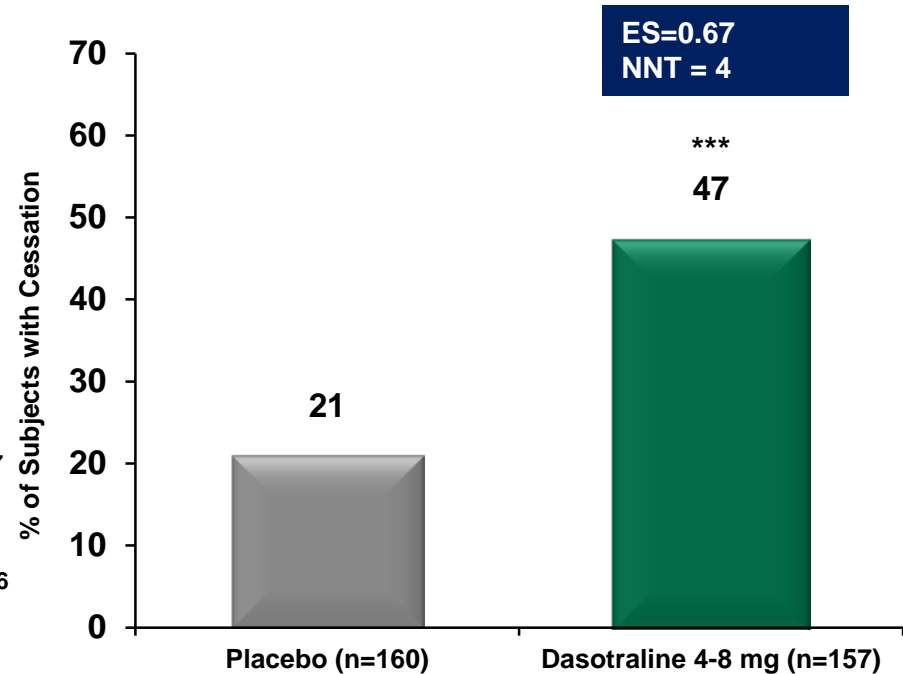
Number of Binge Days per Week



*** $P < 0.0001$ ES=Effect Size

Key Secondary

Percentage of subjects with cessation of bingeing (28 days without bingeing) at week 12



*** $P < 0.0001$

Note: percentage is calculated based on number of subjects at the visit as denominator

Sunovion, Data on file



The Dasotraline Program Continues To Advance

| Study | Timing | Results |
|--|--------------------------------------|--|
| Adult ADHD – only one positive study required | | |
| 201 | December 2013 | Positive study in ADHD |
| 301 | October 2016 | NS – provides supporting evidence |
| Pediatric ADHD – two positive studies required | | |
| 202 | August 2016 | Positive study in Peds ADHD |
| 305 | March 2017 (expected) | Ongoing – results expected March 2017 Completes ADHD submission package |
| BED | | |
| 221 | November 2016 | Positive study in BED |
| 321 | Planned study to start March 2017 | Replication study |

- Plan to submit ADHD (adult & pediatric) NDA in Q2 FY2017
- Plan to submit sNDA for BED in FY2018



SEP-363856



Schizophrenia
Parkinson's disease psychosis



Overview

- Investigational psychotropic agent with non-dopamine D₂ mechanism of action
- Identified by Sunovion researchers in collaboration with PsychoGenics Inc, using its proprietary in vivo SmartCube systems biology drug discovery platform

Indication

- Being studied for patients with ***schizophrenia*** and ***Parkinson's disease psychosis***

Global Phase 2 clinical development program initiated in December 2016

- SEP361-201: 4-week, double-blind, randomized, parallel-group, placebo controlled, flexibly-dosed, multicenter study
 - To evaluate the efficacy and safety of SEP-363856 in acutely psychotic adult subjects with schizophrenia (global) [NCT02969382]
- SEP361-202: 26-week open-label study
 - Safety and tolerability extension study of SEP-363856 in adult subjects with schizophrenia (global) [NCT02970929]
- SEP361-203: Randomized, parallel group, multicenter study
 - To evaluate the efficacy, safety and tolerability of SEP-363856 in subjects with Parkinson's disease psychosis (U.S. only) [NCT02969369]

**NEUROLOGY FRANCHISE
OPPORTUNITIES INCLUDE
EPILEPSY, PARKINSON'S
DISEASE AND STROKE**





APTIOM (eslicarbazepine acetate):

- Voltage-gated sodium channel blocker
 - Member of the dibenzazepine carboxamide family of antiepileptic drugs (AEDs), an established class of medicines
-

APTIOM is approved by the U.S. Food and Drug Administration for adults with partial-onset seizures as:

- Monotherapy (August 27, 2015)
 - Adjunctive therapy (November 8, 2013)
-

Key attributes include:

- Once-daily dosing (not an extended release)
- Crushability
- Not classified as a controlled substance



APTIOM Pediatric Indication for POS

Pursuing an expansion of the indication for APTIOM for the treatment of partial-onset seizures as monotherapy or adjunctive therapy in patients 4 years of age and older

- Submission based on recent FDA guidance that allows extrapolation of data
- Submission will also include:
 - Pediatric data from three trials conducted by our partner BIAL in Europe
 - Pharmacokinetic analyses to support a proposed dosing regimen for children ages 4-17 years

Addresses an unmet need and represents a opportunity for APTIOM

sNDA
submission
anticipated
Q4 FY2016



Apomorphine sublingual film (APL-130277)



OFF episodes associated with Parkinson's disease

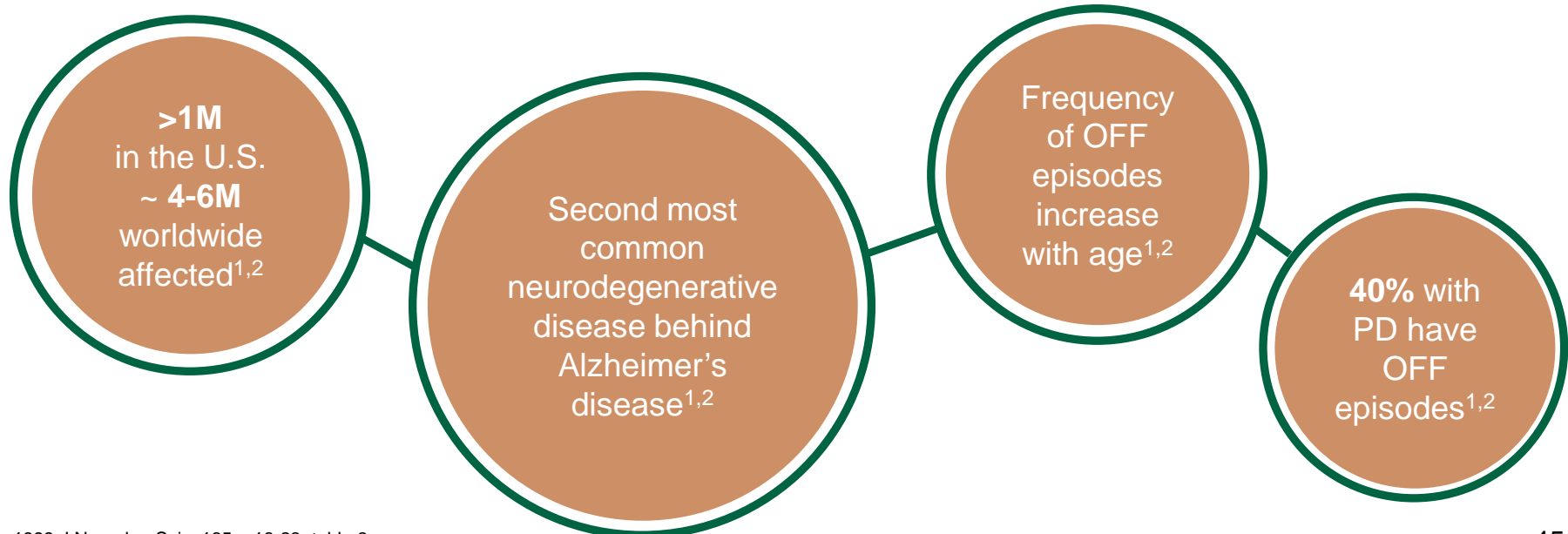


Parkinson's Disease (PD) and OFF Episodes

PD is a chronic, progressive neurodegenerative disease characterized by motor symptoms, rigidity and impaired movement. **OFF episodes** are periods of **loss of function** (motor and non-motor) experienced by PD patients and can occur **one to six times daily**, impairing mobility and **ability to maintain normal activities**.^{1,2}

Types of OFF episodes

- Early morning OFF – patient awakens in OFF state
- Delayed ON – levodopa effects take longer than normal to take effect
- End-of-dose wearing-off – the effects of levodopa wear off prior to next scheduled dose
- Erratic or unpredictable OFF – episode at times not related to dose timing



¹Denny 1999 J Neurolog Sci, v165, p18-23, table 3.

²Schrag 2000 Brain v 123, p2297-2305



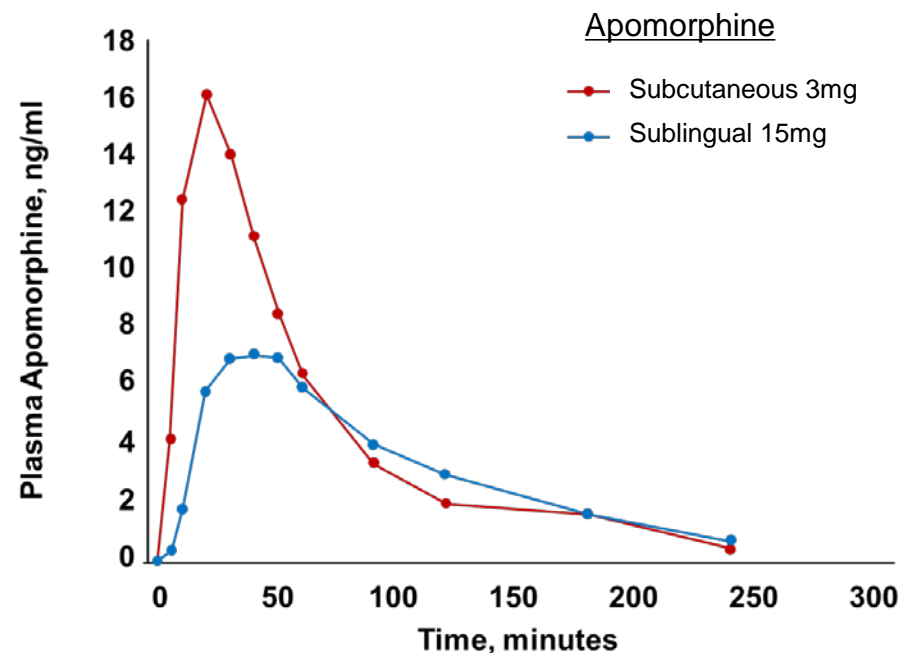
About APL-130277 (sublingual)

Designed to be a fast-acting, easy-to-use thin film for the on-demand management of OFF episodes associated with PD

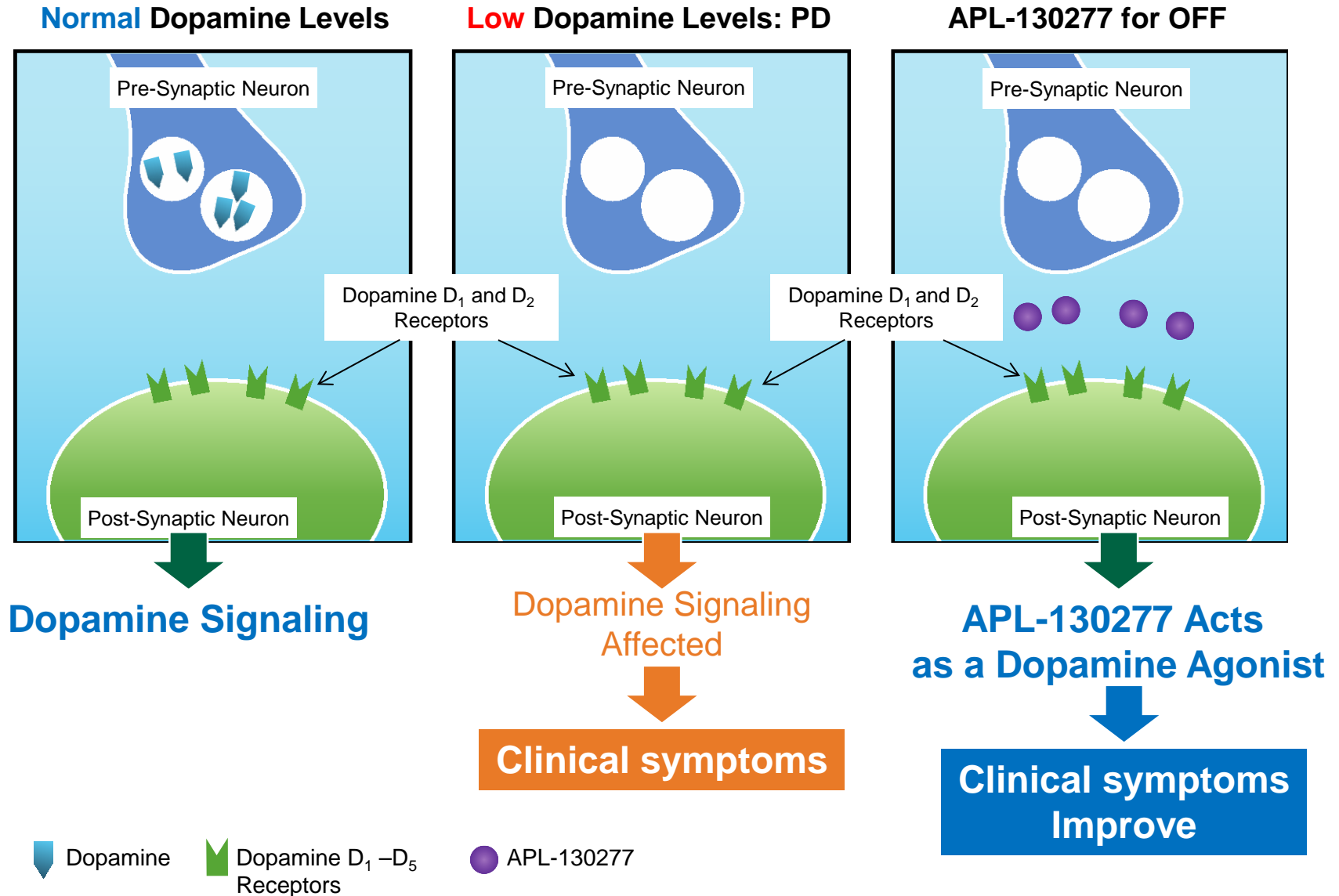
- Novel formulation of apomorphine
- Broad dose range (10 mg – 35 mg being tested)
- Has been studied in all types of OFF episodes, including morning OFF

Single dose pharmacokinetic profile

- Tolerability: blunted peak may relate to low incidence nausea, vomiting, hypotension and possibly low risk QT prolongation
- Efficacy: slow decline in [C] from peak may allow persistence of efficacy
 - In Phase 2 study, approximately 50% of subjects remained “ON” at 90 minutes



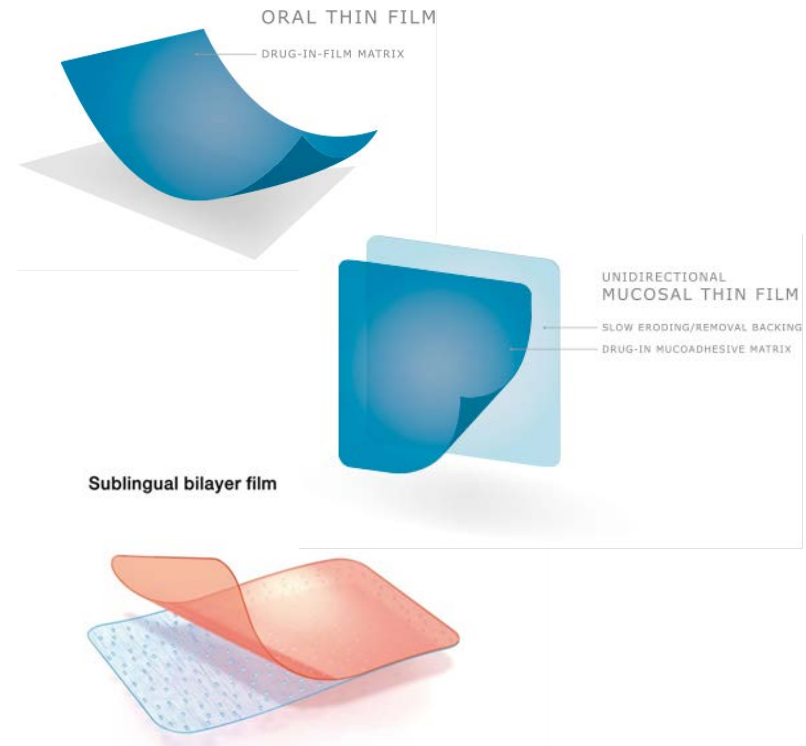
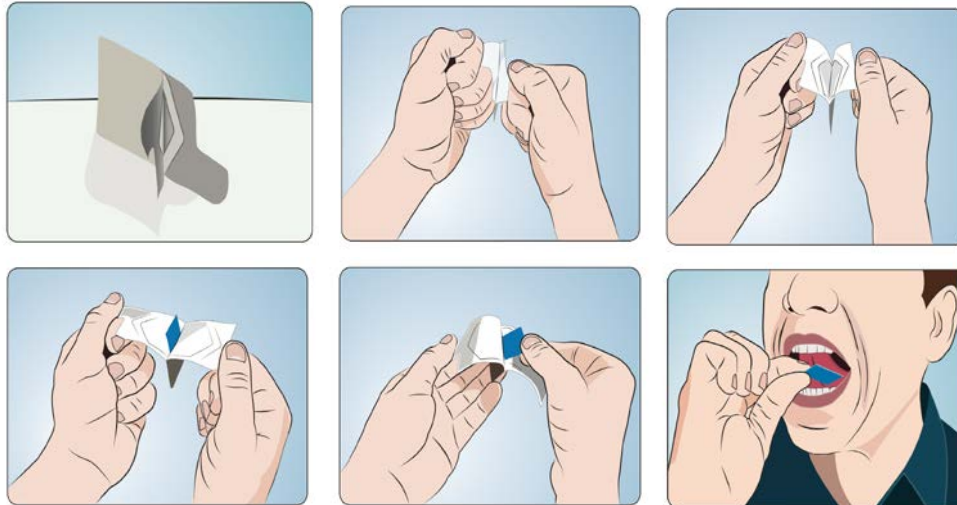
APL-130277: Mechanism of Action





Sublingual (under-the-tongue) administration of apomorphine

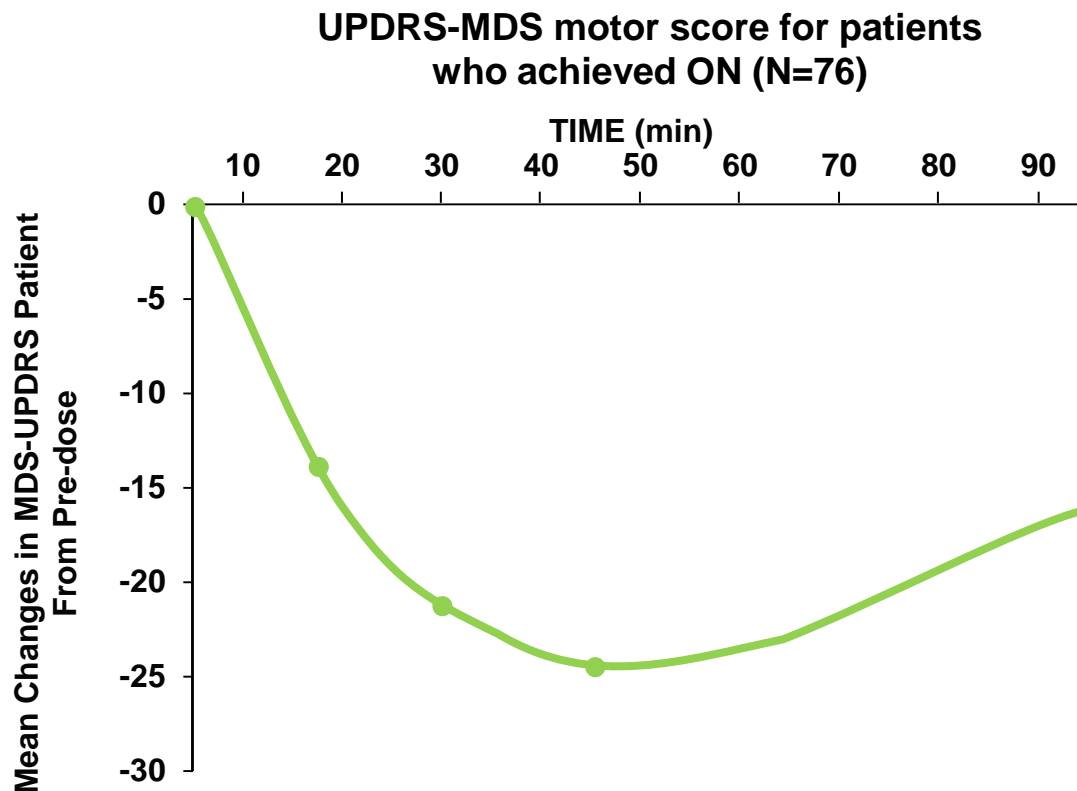
- Designed to be a convenient, well-tolerated, safe and effective option
- May help avoid issues with injectable subcutaneous apomorphine





Open label titration phase study results

- The mean time to full ON as reported by study staff was 22 minutes
- All five doses of APL-130277 (10, 15, 20, 25 and 30 mg) converted patients from the OFF state to a full ON state once titrated to their appropriate dose. Over half of the patients needed the lowest two doses (10 and 15 mg) and 80% used 20 mg or less
- The mean dose required to convert patients to ON was 18.4 mg





CTH-300

- **U.S. double-blind Phase 3 efficacy and safety study**
- Completion is expected in the first half of FY2017

CTH-302

- **European registration has been initiated**
- **Open-label, active comparator study with subcutaneous apomorphine**
- Up to 80 patients randomized in a 4-week open label crossover study
- Primary endpoint is patient preference and quality of life
- The use of an antiemetic should be limited during the study



SB623



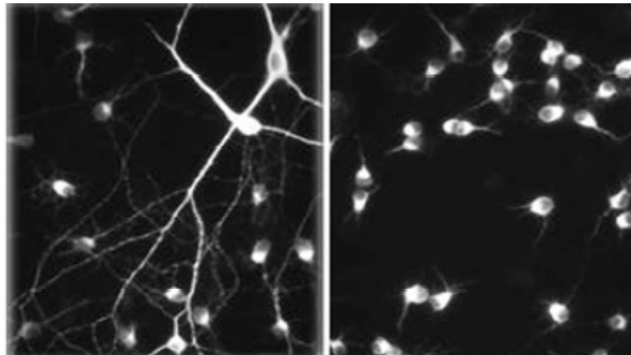
Chronic stroke



Investigational treatment for chronic ischemic stroke

Stem Cells Engineered to Secrete Nerve Growth Factors

25 days tissue culture



SB623

poly-Lysine control

Stereotactic Implantation of Stem Cells Into Brain





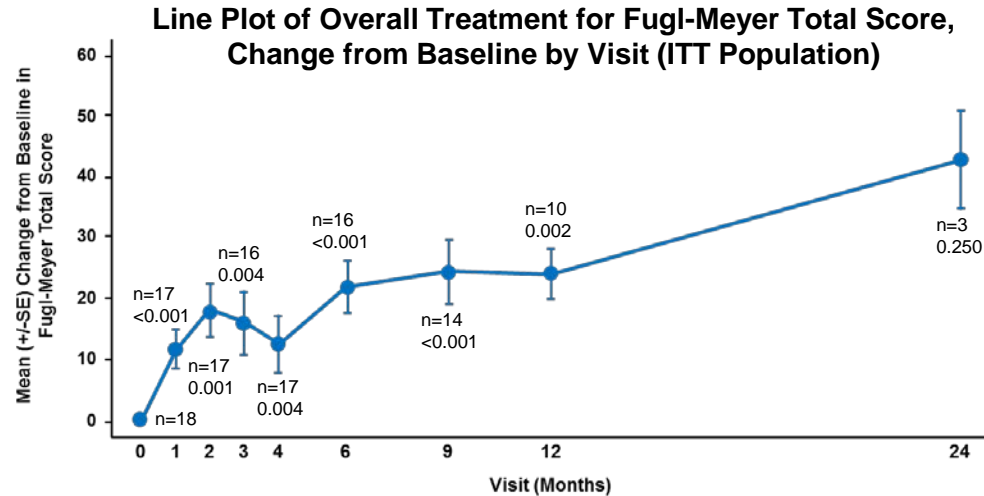
Early Data Supports Ongoing Development

Important Phase 1/2a findings published in *Stroke*

Original Contribution

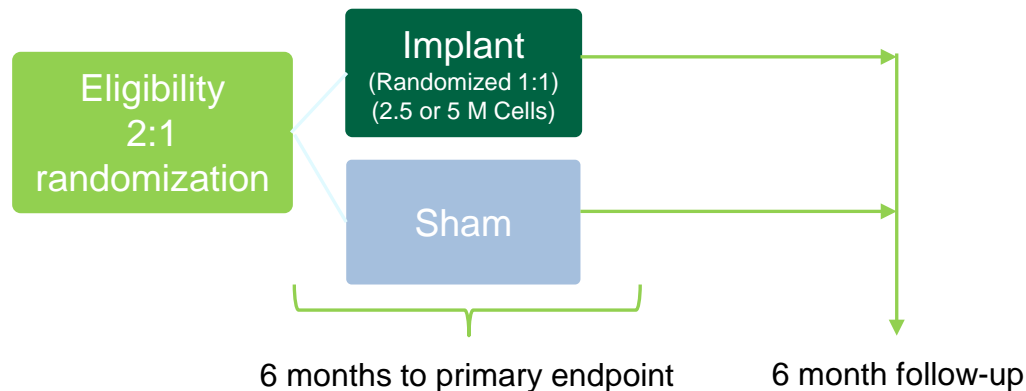
Clinical Outcomes of Transplanted Modified Bone Marrow-Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study

Gary K. Steinberg, MD, PhD; Douglas Kondziolka, MD; Lawrence R. Wechsler, MD; L. Dade Lunsford, MD; Maria L. Coburn, BA; Julia B. Billigen, RN, BS; Anthony S. Kim, MD, MAS; Jeremiah N. Johnson, MD; Damien Bates, MD, PhD; Bill King, MS; Casey Case, PhD; Michael McGrogan, PhD; Ernest W. Yankee, PhD; Neil E. Schwartz, MD, PhD

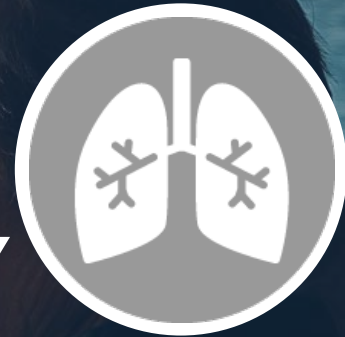


Source: Post-text figure 14.2.4.5
Abbreviations: ITT=intent-to-treat; SE=standard error
Note: p-values were based upon the Wilcoxon Signed Rank test.

Ongoing Phase 2b study design



RESPIRATORY FRANCHISE FOCUSED ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

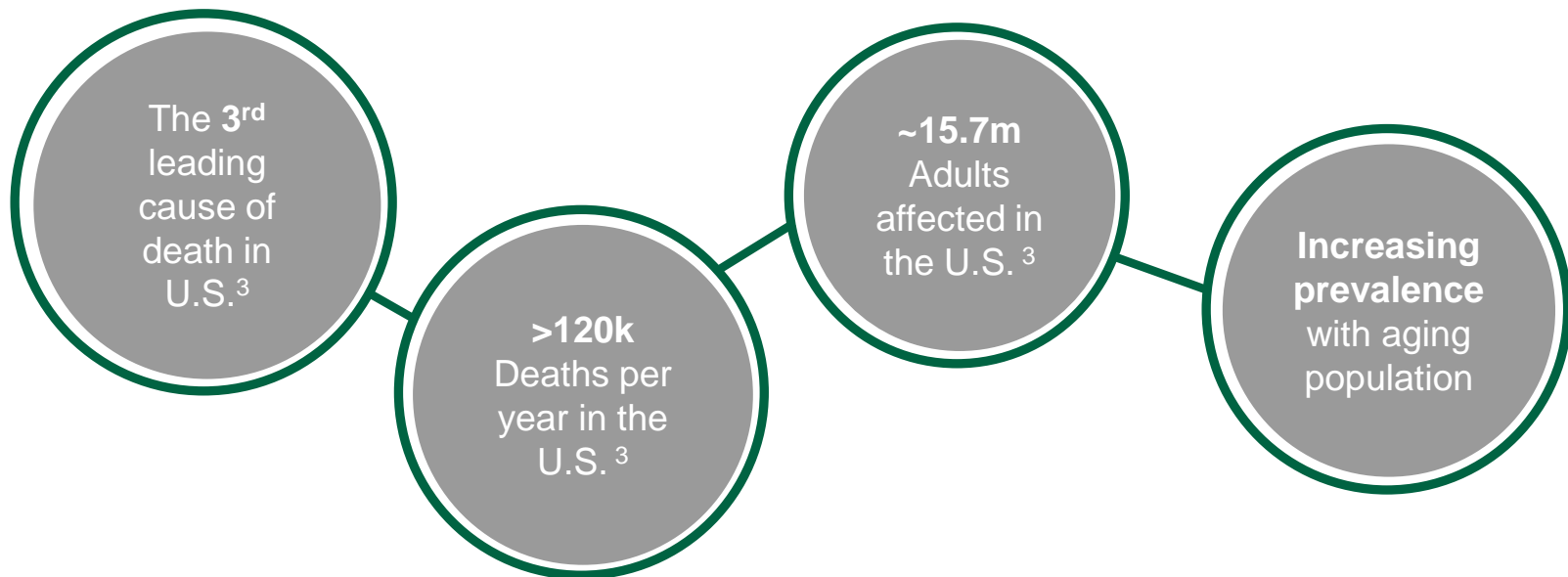


- *Sunovion now has the broadest COPD portfolio in the U.S.*
- *Treatment options for people at all stages of COPD*
- *Flexibility to choose handheld or nebulized products*





COPD is a serious and *progressive respiratory disease* that develops slowly and causes worsening *obstruction of airflow* to the lungs over time,¹ potentially limiting the ability to perform *routine activities*.² Symptoms of COPD include coughing, wheezing, *shortness of breath*, excess production of mucus in the lungs, the inability to breathe deeply and the *feeling of being unable to breathe*.³



¹National Heart, Lung and Blood Institute. What is COPD?




²FDA. Glaxo Appendices.

³MMWR: Morbidity and Mortality Weekly Report. Employment and Activity Limitations Among Adults with Chronic Obstructive Pulmonary Disease.



Disease Severity →



Full trade names are: Seebri™ Neohaler®, Utibron™ Neohaler® and Arcapta® Neohaler®
 ARCAPTA and  are registered trademarks of Novartis AG, used under license
 SEEBRI and  are trademarks of Novartis AG, used under license
 UTIBRON and  are trademarks of Novartis AG, used under license

eFlow® device technology licensed from PARI Pharma GmbH



SUN-101/eFlow[®] (glycopyrronium bromide)



Chronic obstructive pulmonary disease (COPD)



SUN-101/eFlow® is comprised of:

- SUN-101 (glycopyrronium bromide), an investigational, nebulized long-acting muscarinic antagonist (LAMA)
- eFlow®, PARI's innovative investigational closed-system nebulizer customized to deliver SUN-101

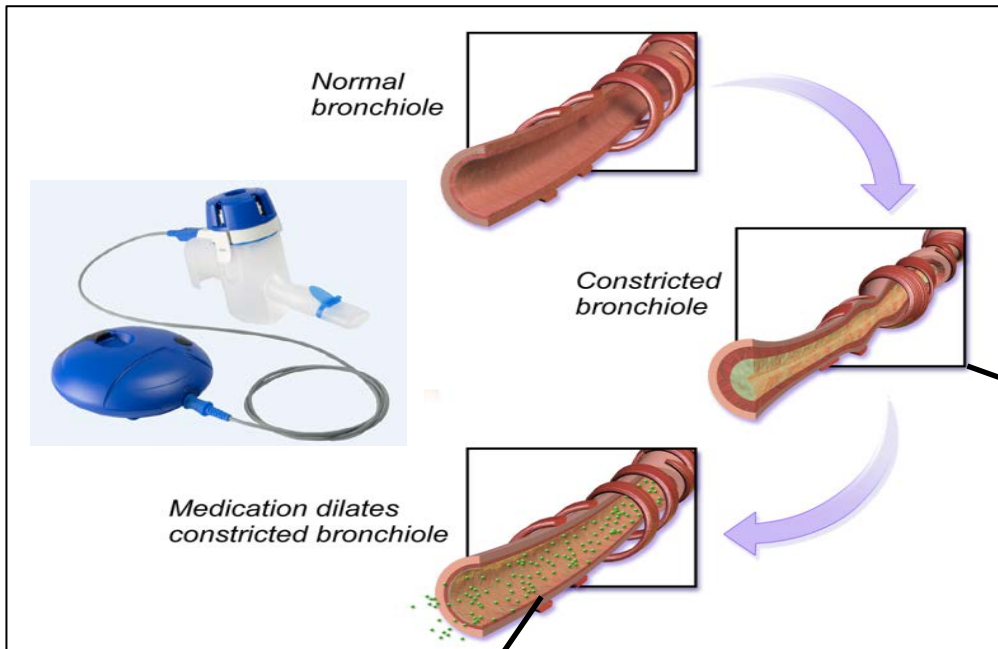
SUN-101/eFlow® is being reviewed by the U.S. Food and Drug Administration (FDA) for the long-term, maintenance treatment of airflow obstruction in patients with COPD

- If approved, it would represent the first available nebulized LAMA for patients with COPD
- May 29, 2017 PDUFA action date

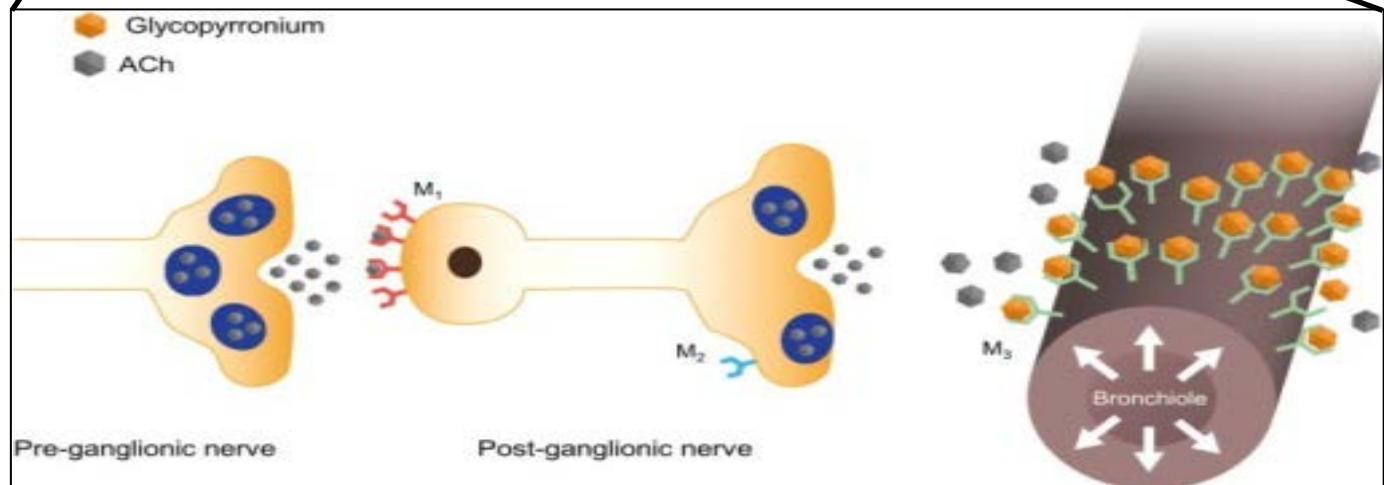
Key attributes include:

- Time for administration is two to three minutes (standard jet nebulizer typically takes up to ten minutes)
- Portable, handheld, electronic system
- Ability for patient to breathe normally

LAMA Mechanism of Action



Long-acting muscarinic antagonist (LAMA) therapies work by blocking M₃ receptors on smooth muscle to produce bronchodilation







GOLDEN-3 and -4 Topline Data

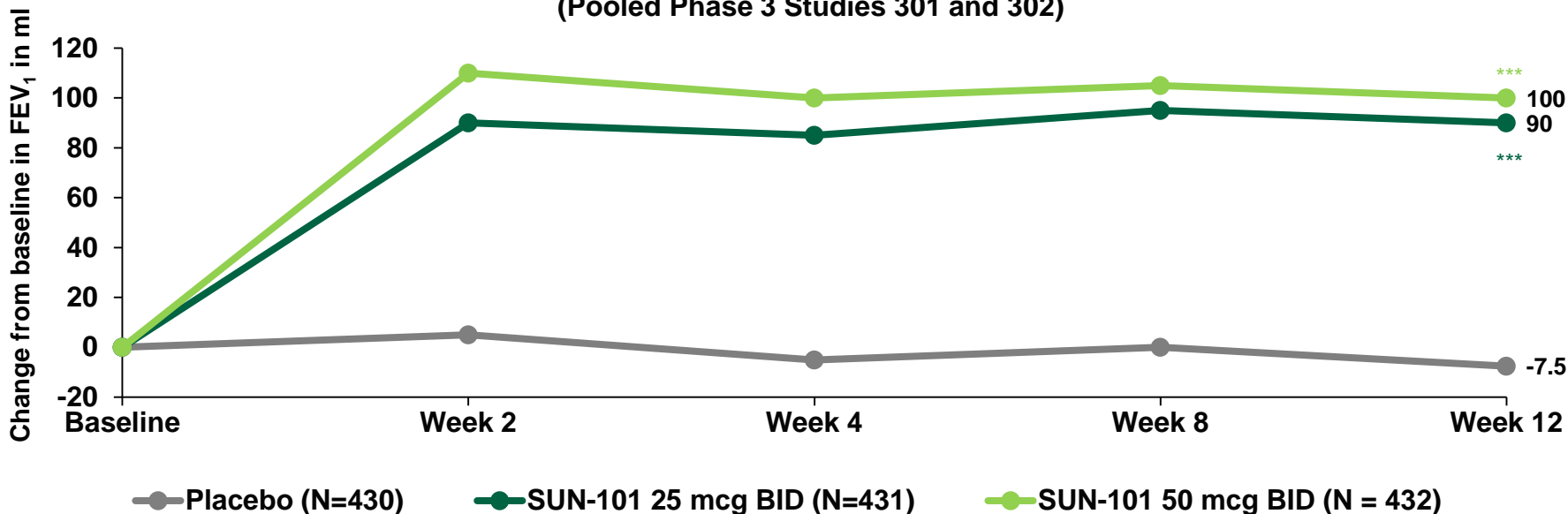
Study Design (SUN101-301 and SUN101-302)

- Overview: Phase 3, 12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter
- Objective: Establish efficacy and safety by comparing SUN-101 twice daily dosing with placebo in adults with moderate-to-very severe COPD
- Enrolled patients: 1294 (GOLDEN-3 and GOLDEN-4 studies) of at least 40 years of age. Included patients with LABA background therapy (30%); and patients with cardiovascular risk factors (65%)
- Primary endpoint: Change from baseline in trough FEV₁ at the end of treatment (week 12)




Study Results

- Efficacy: Statistically significant and clinically important improvements in the primary endpoint in both 25 mcg BID and 50 mcg BID dose groups
- Safety: SUN-101 is safe and generally well tolerated

Mean Change from Baseline in Trough FEV₁ (L) by Visit Week On-Treatment LS Mean SE (95% CI)
(Pooled Phase 3 Studies 301 and 302)



Upcoming Milestones

| Pipeline Progress | FY2016 | FY2017 | FY2018 |
|--|--------|--------|--------|
|  PSYCHIATRY FRANCHISE | | | |
| LATUDA pediatric bipolar depression sNDA expected submission | | ✓ | |
| LATUDA pediatric bipolar depression sNDA expected PDUFA action date | | ✓ | |
| Dasotraline ADHD NDA expected submission | | ✓ | |
| Dasotraline ADHD NDA expected PDUFA action date | | | ✓ |
| Dasotraline ADHD expected launch | | | ✓ |
| Dasotraline BED NDA expected submission | | | ✓ |
|  NEUROLOGY FRANCHISE | | | |
| APTiom pediatric sNDA expected submission | ✓ | | |
| APTiom pediatric sNDA expected PDUFA action date | | ✓ | |
| APL-130277 Ph 3 data | | ✓ | |
| APL-130277 NDA expected submission | | ✓ | |
| APL-130277 expected PDUFA action date | | | ✓ |
| APL-130277 expected launch | | | ✓ |
| TRERIEF (zonisamide) Parkinson's in Dementia with Lewy Bodies sNDA expected submission (Japan) | | ✓ | |
|  RESPIRATORY FRANCHISE | | | |
| Launch UTIBRON Neohaler | | ✓ | |
| Launch SEEBRI Neohaler | | ✓ | |
| Promote ARCAPTA Neohaler | | ✓ | |
| SUN-101/eFlow PDUFA action date | | ✓ | |
| SUN-101/eFlow expected launch | | ✓ | |

New Challenge in Oncology Area; Making Meaningful Medicines

**David J. Bearss, Ph.D.
CEO, Tolero Pharmaceuticals, Inc.**



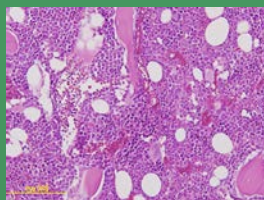
Tolero is committed to developing Meaningful Medicines to improve and extend the lives of patients with serious diseases

Experienced Management Team

| Name/Title | Experience |
|---|--|
| David Bearss, PhD Chief Executive Officer | <ul style="list-style-type: none"> ▪ Founder, CSO at Montigen Pharmaceuticals ▪ CSO at Supergen (Nasdaq: SUPG) ▪ Co-director of the Center for Investigational Therapeutics at the Huntsman Cancer Institute |
| Dallin Anderson, MBA President | <ul style="list-style-type: none"> ▪ Founder, Chairman, CEO and President at Montigen Pharmaceuticals ▪ SVP of Business Development at Supergen (Nasdaq: SUPG) ▪ MBA, Harvard |
| David Sampson, CPA Chief Financial Officer | <ul style="list-style-type: none"> ▪ Vice President of Finance and Principle Accounting Officer, Fusion-io, Inc. ▪ Vice President of Finance, Ancestry.com, Inc. ▪ Audit Senior Manager, Ernst & Young |
| Steve Weitman, MD, PhD Chief Medical Officer | <ul style="list-style-type: none"> ▪ Physician and Director of the Institute for Drug Development, UTHSC-San Antonio ▪ CMO and SVP at Ilex Oncology ▪ Led team for FDA approval of Clofarabine |
| Michael McCullar, PhD, MBA Chief Operating Officer | <ul style="list-style-type: none"> ▪ SVP of Business Development, Astex Pharmaceuticals (Acq. by Otsuka Pharmaceuticals) ▪ Vice President of Strategy and Development, SuperGen, led approval of Dacogen in US, acquisitions of Montigen Pharmaceuticals and Astex Therapeutics, LLC |
| Katsumi Tanaka, MBA Chief Strategy Officer | <ul style="list-style-type: none"> ▪ Senior Officer, Business Development, Sumitomo Dainippon Pharma ▪ Led licensing collaborations with Intercept Pharmaceuticals, SanBio and Edison Pharmaceuticals at Sumitomo Dainippon Pharma |
| Steve Warner, PhD Vice President, Discovery & Development | <ul style="list-style-type: none"> ▪ Translational Genomics Research Institute ▪ Manager, Discovery Biology at Supergen (Nasdaq: SUPG) ▪ Senior Manager, Drug Discovery at the Huntsman Cancer Institute |
| Michael Bernstein, MPH Vice President, Regulatory Affairs | <ul style="list-style-type: none"> ▪ 11 years at the FDA as Project Manager, Administrative Assistant to the Division Director and Executive Secretary to the PCNS and PDAC ▪ Senior Director of Regulatory Affairs at Ilex Oncology ▪ Career to date includes over 20 INDs/CTXs and 9 NDAs/BLAs/MAAs submissions |

Tolero's Meaningful Medicine Approach

AML



- Rapidly progressive disease
- Heterogeneous with tumors harboring multiple different mutations
- No single driver mutation has been identified for the majority of patients
- Patients are older (typically >60 years) and are very sick, limiting the use of toxic therapies



Meaningful Medicine



Alvocidib

+

NOXA
Biomarker

R

ACM

CM

R: Randomize
 ACM: alvocidib + cytarabine + mitoxantrone
 CM: cytarabine + mitoxantrone

High Unmet Medical Needs in AML

- Current standard of care
 - Frontline treatment of AML (naive) : 7+3 regimen
 - Relapsed or refractory (R/R) AML : No standard regimen

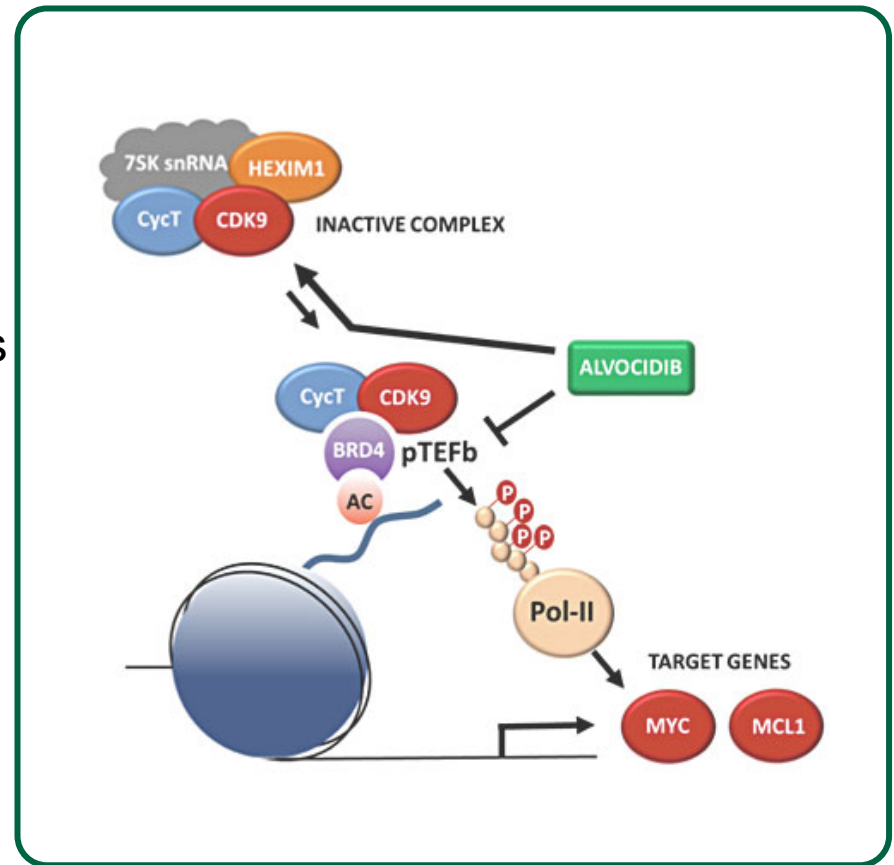
| | Non-elderly | Elderly | | | | | | | | | | | | | | | | | | | | | | | | |
|---|--|---------------------------------|-------------|--------------------------------|-------|------------------------------|-------|--------------------------------|-------|-------------|-------|--------------------------------|------|--|---------------------------------|-------------|-------------|-------|---------------------------------------|-------|--------------------------------|-------|------------------------------|------|---|------|
| naive AML | <p>About 7,000 in US</p> <table border="1"> <thead> <tr> <th>Systemic Therapy(Induction)</th> <th>utilization</th> </tr> </thead> <tbody> <tr> <td>7+3 (cytarabine, daunorubicin)</td> <td>36.9%</td> </tr> <tr> <td>7+3 (cytarabine, idarubicin)</td> <td>29.2%</td> </tr> <tr> <td>5+2 (cytarabine, idarubicin)</td> <td>6.5%</td> </tr> <tr> <td>azacitidine</td> <td>6.0%</td> </tr> <tr> <td>5+2 (cytarabine, daunorubicin)</td> <td>3.5%</td> </tr> </tbody> </table> <p>CR rate : 54.7%</p> | Systemic Therapy(Induction) | utilization | 7+3 (cytarabine, daunorubicin) | 36.9% | 7+3 (cytarabine, idarubicin) | 29.2% | 5+2 (cytarabine, idarubicin) | 6.5% | azacitidine | 6.0% | 5+2 (cytarabine, daunorubicin) | 3.5% | <p>About 10,000 pts in US</p> <table border="1"> <thead> <tr> <th>Systemic Therapy(Induction)</th> <th>utilization</th> </tr> </thead> <tbody> <tr> <td>azacitidine</td> <td>31.1%</td> </tr> <tr> <td>decitabine</td> <td>14.3%</td> </tr> <tr> <td>7+3 (cytarabine, daunorubicin)</td> <td>13.6%</td> </tr> <tr> <td>7+3 (cytarabine, idarubicin)</td> <td>9.4%</td> </tr> <tr> <td>LoDAC</td> <td>7.4%</td> </tr> </tbody> </table> <p>CR rate : 30.3%</p> | Systemic Therapy(Induction) | utilization | azacitidine | 31.1% | decitabine | 14.3% | 7+3 (cytarabine, daunorubicin) | 13.6% | 7+3 (cytarabine, idarubicin) | 9.4% | LoDAC | 7.4% |
| | Systemic Therapy(Induction) | utilization | | | | | | | | | | | | | | | | | | | | | | | | |
| 7+3 (cytarabine, daunorubicin) | 36.9% | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7+3 (cytarabine, idarubicin) | 29.2% | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5+2 (cytarabine, idarubicin) | 6.5% | | | | | | | | | | | | | | | | | | | | | | | | | |
| azacitidine | 6.0% | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5+2 (cytarabine, daunorubicin) | 3.5% | | | | | | | | | | | | | | | | | | | | | | | | | |
| Systemic Therapy(Induction) | utilization | | | | | | | | | | | | | | | | | | | | | | | | | |
| azacitidine | 31.1% | | | | | | | | | | | | | | | | | | | | | | | | | |
| decitabine | 14.3% | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7+3 (cytarabine, daunorubicin) | 13.6% | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7+3 (cytarabine, idarubicin) | 9.4% | | | | | | | | | | | | | | | | | | | | | | | | | |
| LoDAC | 7.4% | | | | | | | | | | | | | | | | | | | | | | | | | |
| R/R AML | <p>About 4,000 pts in US</p> <table border="1"> <thead> <tr> <th>Systemic Therapy(First relapse)</th> <th>utilization</th> </tr> </thead> <tbody> <tr> <td>FLAG-ida</td> <td>19.5%</td> </tr> <tr> <td>HiDAC</td> <td>13.6%</td> </tr> <tr> <td>7+3 (cytarabine, daunorubicin)</td> <td>12.8%</td> </tr> <tr> <td>azacitidine</td> <td>10.1%</td> </tr> <tr> <td>MEC</td> <td>9.0%</td> </tr> </tbody> </table> <p>CR rate : 31.7% (first relapse)</p> | Systemic Therapy(First relapse) | utilization | FLAG-ida | 19.5% | HiDAC | 13.6% | 7+3 (cytarabine, daunorubicin) | 12.8% | azacitidine | 10.1% | MEC | 9.0% | <p>About 5,000 pts in US</p> <table border="1"> <thead> <tr> <th>Systemic Therapy(First relapse)</th> <th>utilization</th> </tr> </thead> <tbody> <tr> <td>azacitidine</td> <td>25.8%</td> </tr> <tr> <td>Investigational drug (clinical trial)</td> <td>16.2%</td> </tr> <tr> <td>decitabine</td> <td>10.9%</td> </tr> <tr> <td>LoDAC</td> <td>8.2%</td> </tr> <tr> <td>7+3+7 (cytarabine, daunorubicin, etoposide)</td> <td>5.9%</td> </tr> </tbody> </table> <p>CR rate : 21.1% (first relapse)</p> | Systemic Therapy(First relapse) | utilization | azacitidine | 25.8% | Investigational drug (clinical trial) | 16.2% | decitabine | 10.9% | LoDAC | 8.2% | 7+3+7 (cytarabine, daunorubicin, etoposide) | 5.9% |
| Systemic Therapy(First relapse) | utilization | | | | | | | | | | | | | | | | | | | | | | | | | |
| FLAG-ida | 19.5% | | | | | | | | | | | | | | | | | | | | | | | | | |
| HiDAC | 13.6% | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7+3 (cytarabine, daunorubicin) | 12.8% | | | | | | | | | | | | | | | | | | | | | | | | | |
| azacitidine | 10.1% | | | | | | | | | | | | | | | | | | | | | | | | | |
| MEC | 9.0% | | | | | | | | | | | | | | | | | | | | | | | | | |
| Systemic Therapy(First relapse) | utilization | | | | | | | | | | | | | | | | | | | | | | | | | |
| azacitidine | 25.8% | | | | | | | | | | | | | | | | | | | | | | | | | |
| Investigational drug (clinical trial) | 16.2% | | | | | | | | | | | | | | | | | | | | | | | | | |
| decitabine | 10.9% | | | | | | | | | | | | | | | | | | | | | | | | | |
| LoDAC | 8.2% | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7+3+7 (cytarabine, daunorubicin, etoposide) | 5.9% | | | | | | | | | | | | | | | | | | | | | | | | | |

Alvocidib Can Be a Meaningful Medicine

- Potential to improve the rate of complete remissions in patients with AML
 - Consistent and promising activity in both frontline and relapsed or refractory AML
 - Significant clinical experience in over 400 patients with AML
- Biomarker enables identification of patients likely to respond to alvocidib
- Potent inhibitor of CDK9 which regulates the transcription of many important proteins such as MCL1, which are involved with cancer

Alvocidib Disrupts Super Enhancer Activity via CDK9 Inhibition

- Alvocidib is a potent inhibitor of CDK9
- Alvocidib downregulates transcription of super enhancer-regulated genes, such as c-Myc and MCL1
- MCL1 is an important survival factor in many forms of cancer including AML



Alvocidib in AML

- The complex nature of AML suggests combination therapy would be more effective than single agents
- Investigators at the National Cancer Institute (NCI) identified alvocidib as an encouraging novel agent to be used in combination AML therapy
 - Alvocidib targets key pathways involved with AML – differentiated from cytotoxic therapies
 - Synergistic when used in Timed Sequential Therapy (TST)
- Alvocidib has consistently shown encouraging activity in multiple AML studies as part of the regimen

ACM: alvocidib, cytarabine, mitoxantrone

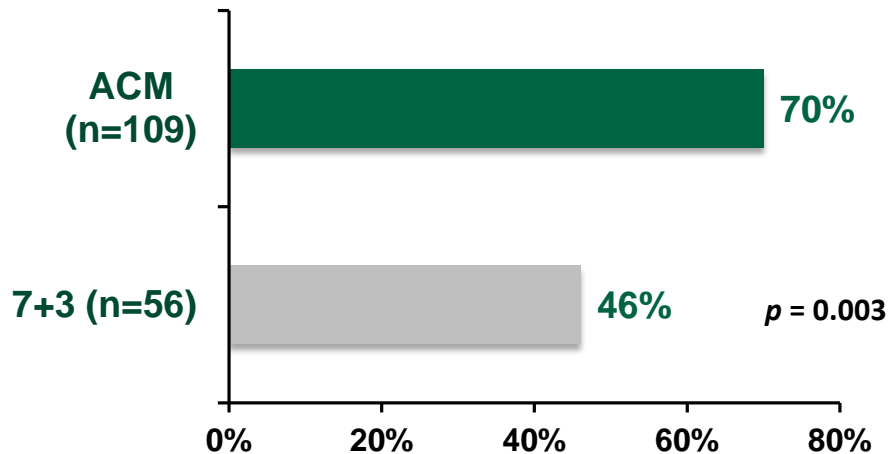
Phase 2 Study Results (Efficacy) (Conducted by NCI)

Positive randomized Phase 2 study in naive poor-risk AML patients

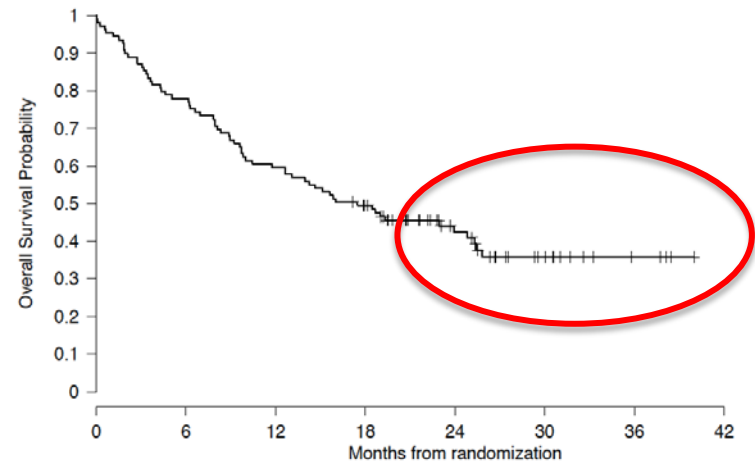
- Most patients had secondary AML or other poor-risk features
- ACM demonstrated a statistically significant improvement in CR rate Over 7+3 (standard of care)

- Survival plateaued in a high proportion of ACM-treated patients

CR Rate: ACM vs. 7+3



Survival of ACM-Treated Patients



ACM advantage was consistent across subgroups including adverse cytogenetics, FLT3, secondary AML

Phase 2 Study Results (Safety) (Conducted by NCI)

- ACM demonstrated similar tolerability as control therapy

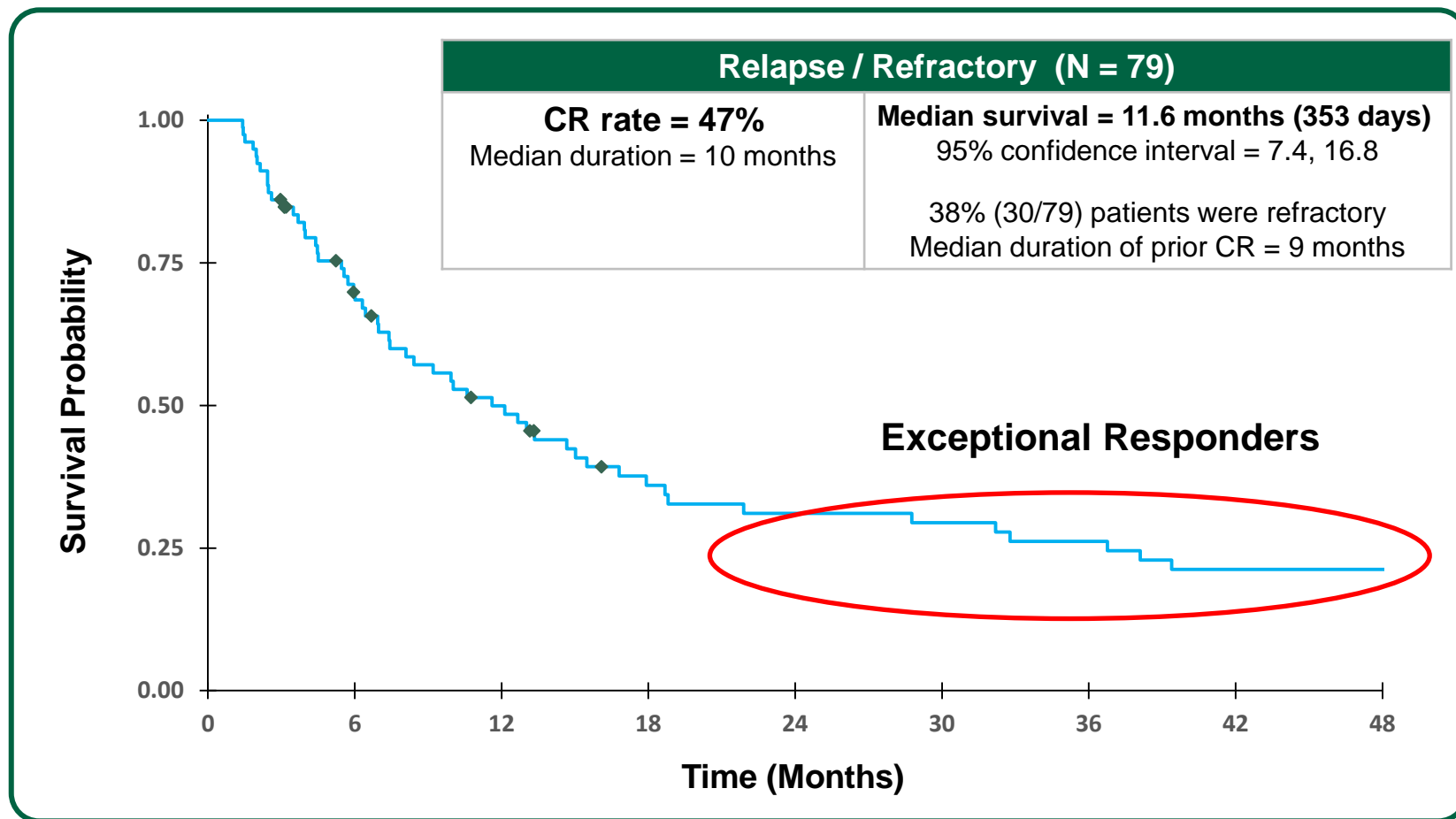
- **naive poor-risk AML patients**

| Grade ≥ 3 toxicity | ACM (n=109) | 7+3 (n=56) | p |
|----------------------------|-------------|------------|-------|
| Tumor lysis syndrome | 9 (8%) | 4 (7%) | >0.99 |
| Myocardial dysfunction | 8 (7%) | 3 (5%) | 0.75 |
| GI toxicity | 12 (11%) | 5 (9%) | 0.79 |
| Hepatic dysfunction | 23 (21%) | 13 (23%) | 0.84 |
| Infection | 38 (35%) | 21 (38%) | 0.74 |
| Pulmonary toxicity | 8 (7%) | 4 (7%) | >0.99 |
| Renal toxicity | 3 (3%) | 1 (2%) | >0.99 |
| Thromboembolic events | 3 (3%) | 1 (2%) | >0.99 |
| Febrile neutropenia events | 52 (48%) | 25 (45%) | 0.74 |

Joshua F. Zeidner, et al. *haematologica* 2015; 100: 1172.

Phase 1 & 2 Study Results (Pooled Analysis)

Phase 1 & 2 R/R AML studies overall survival – pooled analysis

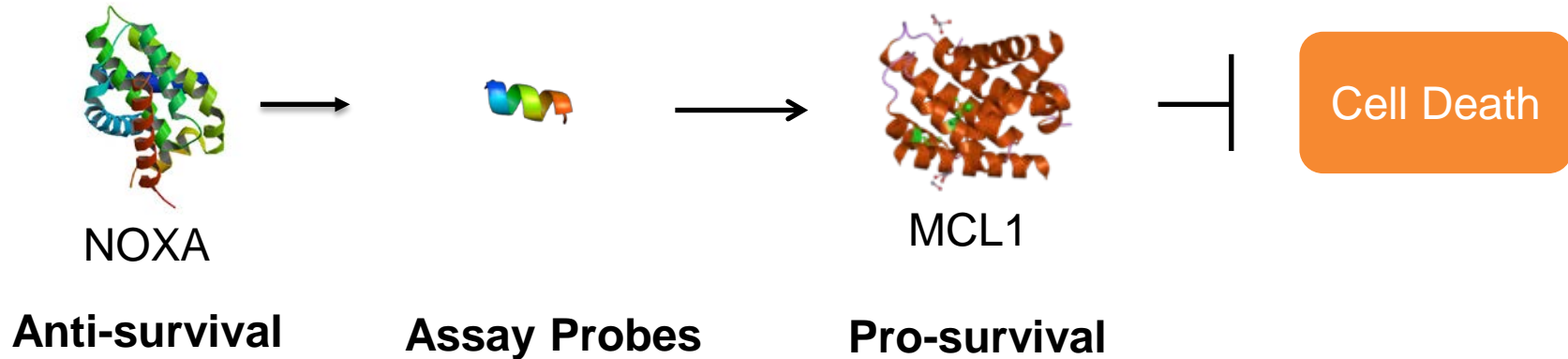


Alvocidib in MCL1-Dependent Malignancies

- Alvocidib's primary pharmacology is related to potent inhibition of CDK9
- CDK9 is a central signaling protein in the super enhancer complex
- By inhibiting CDK9, alvocidib can disrupt super enhancer-driven expression of MCL1
- The ability of alvocidib to prevent the expression of MCL1 may provide a novel approach to targeting MCL1-dependent malignancies

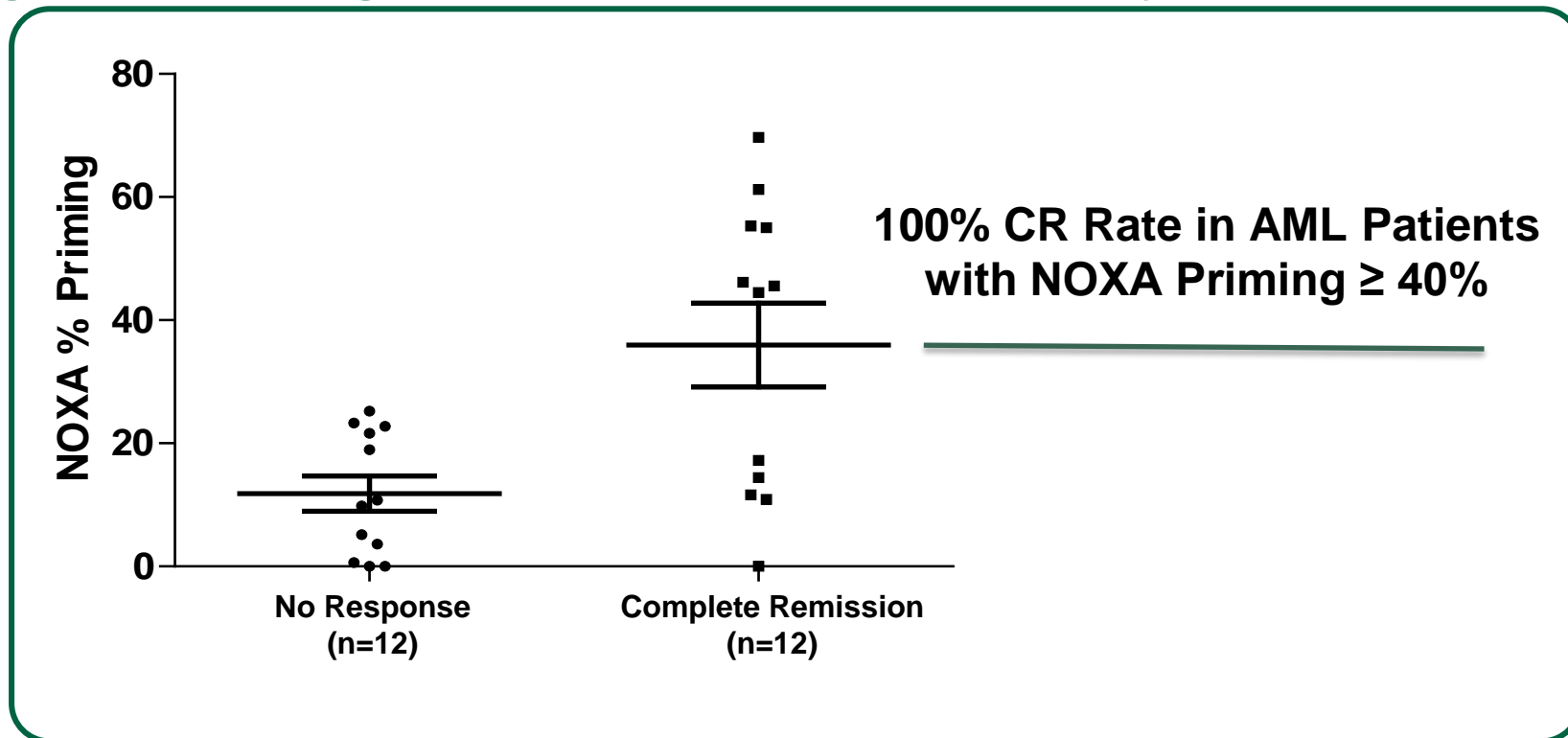
Functional Approach to Determine MCL1 Dependency

- MOA of alvocidib can be leveraged into an assay platform to identify sensitive patients
- MCL1 is a key survival signal well documented in AML
- NOXA is anti-survival protein inhibiting MCL1
- NOXA priming is a functional measurement of MCL1 dependence in AML



Results from NOXA Priming Validation Set

High NOXA priming is predictive of alvocidib sensitivity in AML patients



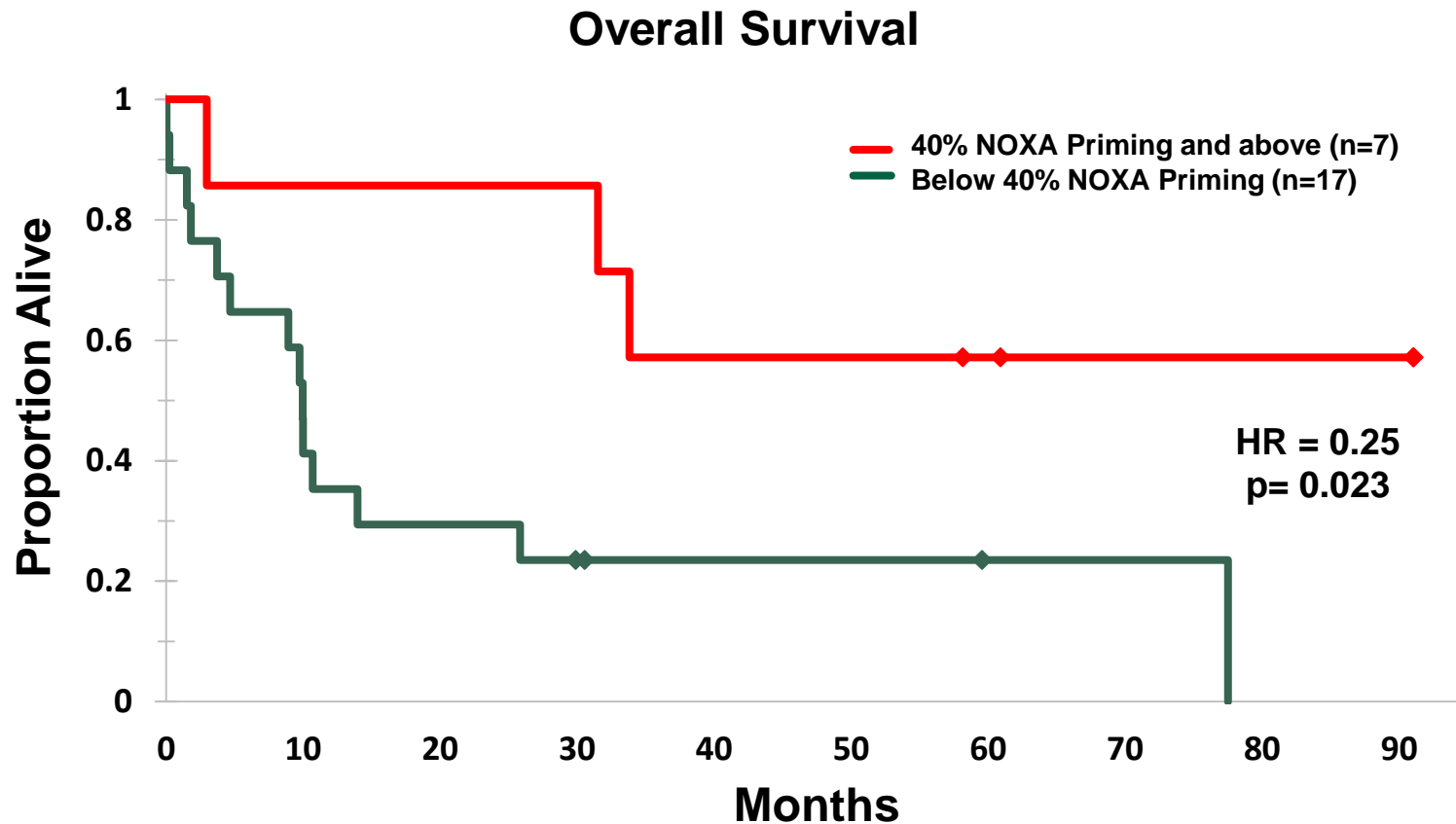
NOXA priming in CR and NR (No Response) pre-treatment bone marrow samples from AML patients treated with the ACM regimen

NOXA priming did not predict response in patients treated with 7+3

25% of AML patients are positive for the biomarker

Overall Survival in ACM-Treated AML Patients

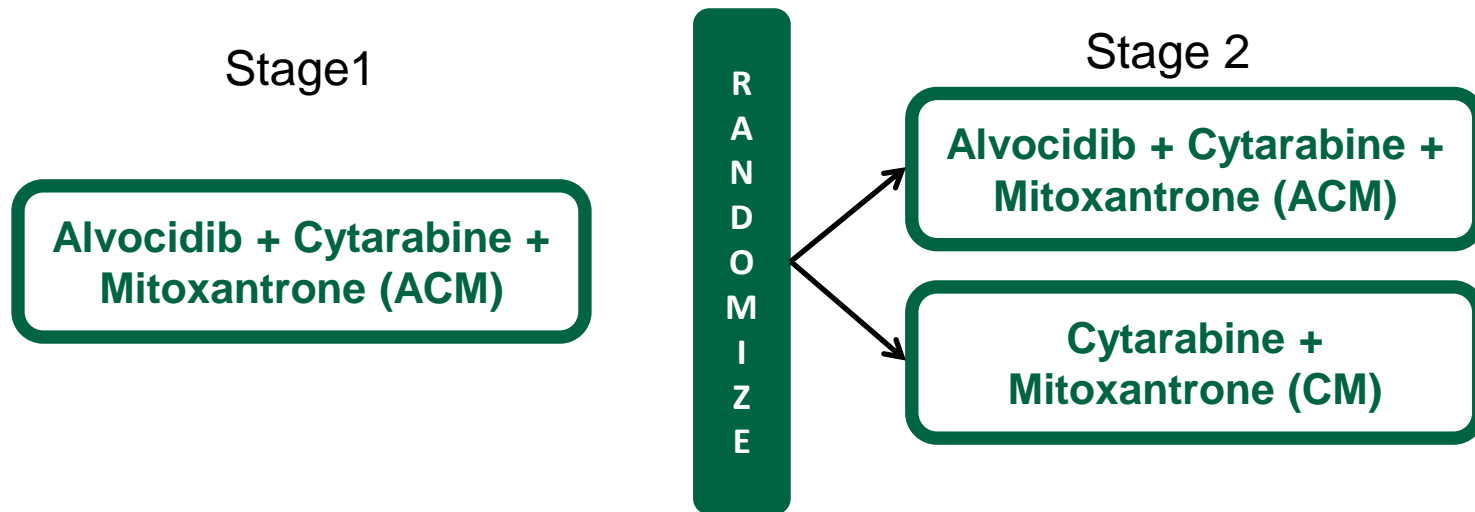
ACM-treated AML patients with NOXA priming greater than 40% demonstrated greater survival



Phase 2 Study Design (Biomarker)

● Biomarker-driven Phase 2 AML Study:

- Two-stage Phase 2 study; Open-label, randomized study to assess the clinical response to ACM compared to AM treatment in relapsed or refractory AML patients (18-65 years) with MCL1 positive patients
 - * MCL1 positive patients: Method of measuring using biomarker (NOXA priming)
- Primary endpoint: Complete remission rate
- Secondary endpoint: Overall survival rate, etc.
- Study Start Date : December 2015



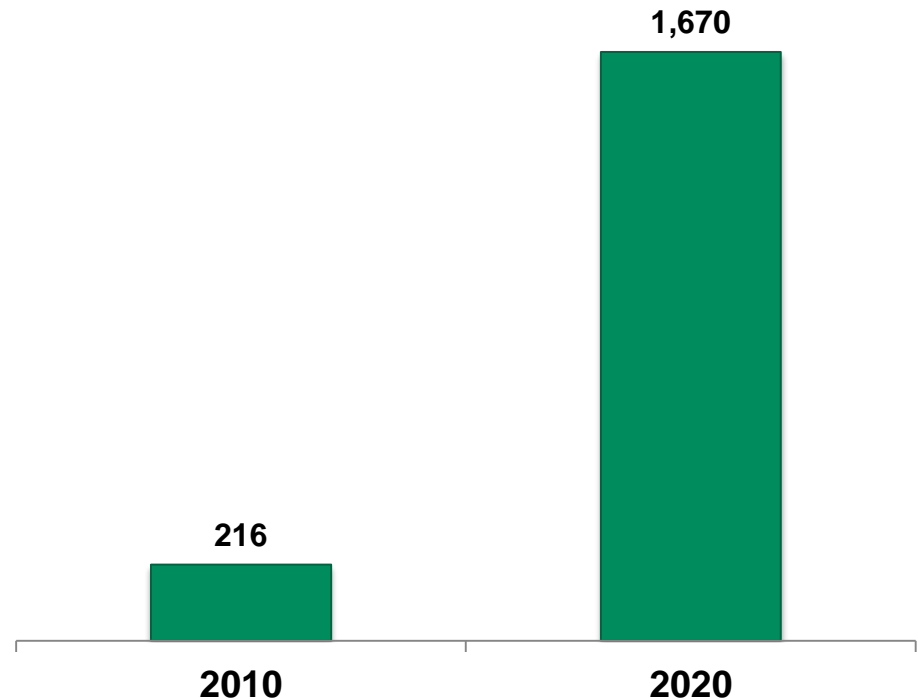
Positive FDA Guidance

- FDA agreed that a single, randomized trial in patients with relapse or refractory AML, with CR rate as the primary endpoint, would support NDA
 - Statistical significance on CR rate will support accelerated approval
 - Tolero expects to have data from the biomarker-driven Phase 2 study which would support an NDA filing in FY2018
 - Tolero plans to consult this strategy with the FDA based on stage 1 data of Phase 2
- Tolero will perform a confirmatory study with OS as the primary endpoint
 - Confirmatory study may be done in a different patient population such as frontline AML
 - Tolero expects to have the confirmatory study underway in 2018
- Analysis of OS will include patients who have received a stem cell transplant, censoring only those patients alive at the time of the final analysis
 - Primary analysis of OS regardless of transplant, with a sensitivity analysis censored for transplant. This approach is advantageous, as it will favor treatments that attain a high CR rate

AML Market Positioned for Rapid Growth

- AML therapies have remained unchanged for decades
- As evidenced in other liquid tumors, therapies offering new mechanisms should experience rapid adoption
- Frontline AML and relapsed or refractory AML addresses 75,000 patients in the major markets

AML Market to Experience Rapid Growth (Revenue, \$M, G8 Countries)



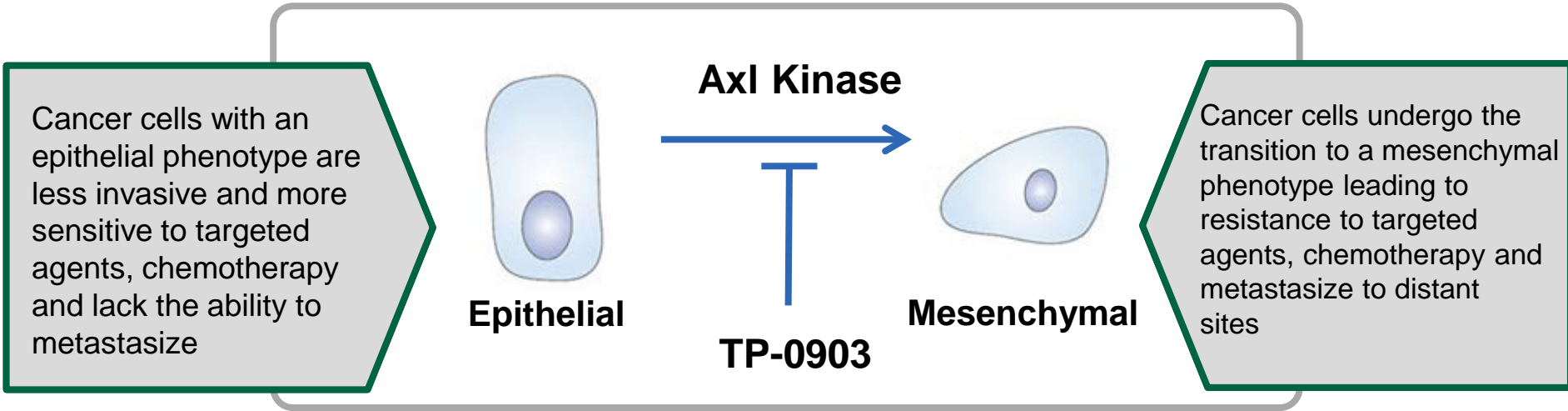
Source: *thepharmaletter*, 20-12-2011

Tolero Pipeline

| Program | Mechanism of action | Target indication | Pre-clinical | Phase 1 | Phase 2 | Phase 3 |
|-----------|-------------------------------|---|--------------|---------|---------|---------|
| Alvocidib | CDK9 inhibitor | Biomarker-Defined R/R AML | | | | |
| | | Biomarker-Defined MDS | | | | |
| | | Frontline AML (Combination therapy with 7+3) | | | | |
| TP-0903 | Axl Kinase Inhibitor | TBD | | | | |
| TP-1287 | Oral CDK9 Inhibitor | TBD | | | | |
| TP-0184 | ALK2/BMPR Signaling Inhibitor | TBD | | | | |

TP-0903: Axl Kinase Inhibitor

TP-0903 blocks the mesenchymal phenotype in cancer cells



Hallmarks of a Mesenchymal Phenotype

| | | |
|-----------------|---------------------------------|---|
| Drug Resistance | Escape From Immune Surveillance | Resist Endogenous Differentiation Signals |
|-----------------|---------------------------------|---|

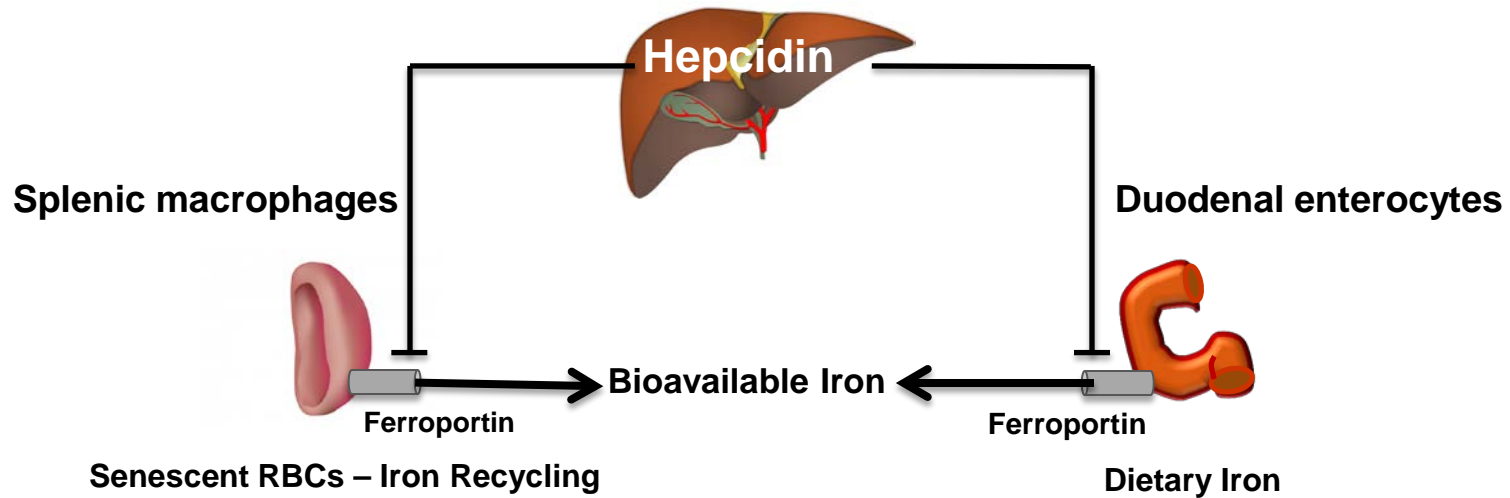
TP-0903: Program Summary

- Phase 1 study enrolling
- TP-0903 is a first in class inhibitor of AXL
- Inhibition of AXL targets several key cancer pathways through inhibition of the mesenchymal phenotype
 - Restores sensitivity to targeted therapies
 - Synergistic with PD-L1 inhibition
- Favorable drug-like properties and pharmaceutical profile
- Multiple tumor types to explore for development in major indications

Tolero Pipeline

| Program | Mechanism of action | Target indication | Pre-clinical | Phase 1 | Phase 2 | Phase 3 |
|-----------|----------------------------------|---|--------------|------------|------------|------------|
| Alvocidib | CDK9 inhibitor | Biomarker-Defined R/R AML | ██████████ | ██████████ | ██████████ | ██████████ |
| | | Biomarker-Defined MDS | ██████████ | ██████████ | ██████████ | ██████████ |
| | | Frontline AML (Combination therapy with 7+3) | ██████████ | ██████████ | ██████████ | ██████████ |
| TP-0903 | Axl Kinase Inhibitor | TBD | ██████████ | ██████████ | ██████████ | ██████████ |
| TP-1287 | Oral CDK9 Inhibitor | TBD | ██████████ | ██████████ | ██████████ | ██████████ |
| TP-0184 | ALK2/BMPR Signaling Inhibitor | TBD | ██████████ | ██████████ | ██████████ | ██████████ |

Hepcidin – A Master Regulator of Iron Levels in the Blood



- Hepcidin is a peptide liver hormone that binds to the iron export pump, ferroportin, and sequesters iron making it unavailable to support erythropoiesis
- Hepcidin becomes up regulated during inflammation resulting in functional iron deficiency
- Hepcidin-lowering agents represent a novel approach to treating anemia of chronic disease

TP-0184: ALK2/BMPR Signaling Inhibitor

- TP-0184 demonstrates anti-anemia in vivo activity
 - Downregulates circulating hepcidin levels
 - Increases serum iron in inflammatory models
 - Improves hemoglobin levels in models of anemia
 - Concentrates in the liver, its target site of action
- Multiple pathways of development
 - Cancer – supportive care
 - Anemia of chronic disease/inflammation
- Expected Differentiation:
ALK2/BMPR targeting activity allows for an anti-anemia through oral delivery of a small molecule
- Selected as a lead candidate to enter IND track
- Good pharmaceutical properties and wide therapeutic window

Disclaimer Regarding Forward-looking Statements

The statements made in this presentation material are forward looking statements based on management's assumptions and beliefs in light of information available up to the day of announcement, and involve both known and unknown risks and uncertainties.

Actual financial results may differ materially from those presented in this document, being dependent on a number of factors.

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