

# Strongbridge Biopharma plc

October 2018

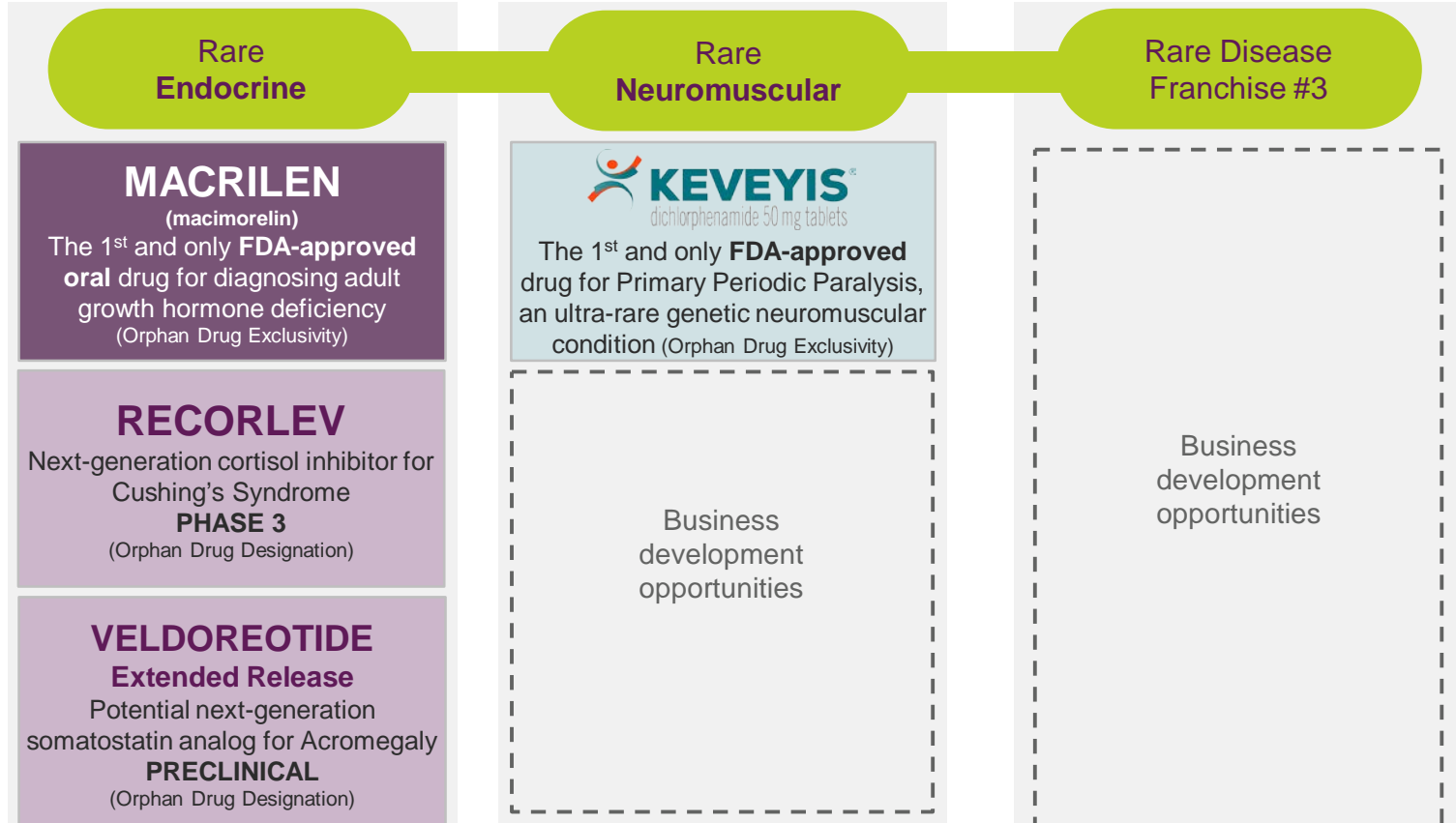
# Forward-looking statements

This document contains forward-looking statements relating to the Company's strategy, objectives, business development plans and financial position. All statements other than statements of historical facts included in this document, including, without limitation, statements regarding the Company's future financial position, strategy, anticipated investments, costs and results, status and results of clinical trials, size of patient population, plans, outcomes of product development efforts, intellectual property portfolio and objectives of management for future operations, may be deemed to be forward-looking statements. You can identify forward-looking statements by words such as "anticipate," "believe," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "will," "would" or the negative of those terms, and similar expressions that convey uncertainty or future events or outcomes.

These forward-looking statements involve known and unknown risks, uncertainties, and other factors that may cause the Company's actual results, performance, or achievements or industry results to be materially different from those contemplated, projected, forecasted, estimated or budgeted, whether expressed or implied, by these forward-looking statements. Given these risks and uncertainties, investors should not place undue reliance on forward-looking statements as a prediction of actual results. A discussion of certain of these risks may be found in the filings the Company makes with the U.S. Securities and Exchange Commission. None of these forward-looking statements constitutes a guarantee of the future occurrence of such events or of actual results. These statements are based on data, assumptions, and estimates that the Company believes are reasonable.

The forward-looking statements contained in this document are made only as of the date hereof. Except as otherwise required by law, the Company expressly disclaims any obligation or undertaking to release publicly any updates of any forward-looking statements contained in this document to reflect any change in its actual results, assumptions, expectations or any change in events, factors, conditions, or circumstances on which any forward-looking statement contained in this document is based.

# Strongbridge Biopharma plc: Building a portfolio of therapeutically-aligned vertical franchises in rare diseases



# Recent and anticipated milestones

2H - 2018

**Macrilen**

Commercial launch (July 2018)

**Recorlev**

**SONICS** Top-line data (August 2018)  
**SONICS** Additional data (Q4 2018)

**Keveyis**

Quarterly sales updates

**Corporate**

Q2 2018 & Q3 2018 earnings

1H -2019

Quarterly sales updates

**SONICS** Top-line one-year data (Q1 2019)  
**LOGICS** Top-line data (Q1 2019)

Quarterly sales updates

Q4 2018 & Q1 2019 earnings

# Recorlev

(levoketoconazole)

# Cushing's syndrome complications and comorbidities

Psychosis, impaired memory, sleep disturbance, depression, anxiety

Heart attacks, stroke, high blood pressure, high cholesterol, vein clots

Overweight/obesity, facial, neck and abdominal fat accumulation, diabetes

Muscle and skin atrophy

Osteoporosis

Compared to those without Cushing's disease, young patients have:<sup>1\*</sup>

**2-5x** higher incidence rates of comorbidities (eg, cardiovascular, endocrine, musculoskeletal, and mental health conditions)

**7x** higher medical costs

**4x** higher pharmacy costs

Source: Company sponsored research and published research including Feelders RA, Hofland LJ. (J Clin Endoc Metab. 2013;98(2):425-438) and Daly et al. (J Clin Endoc Metab 2006) \*According to a retrospective analysis of claims from a large US commercial health plan (885 selected Cushing's disease cases and 2,655 matched controls without Cushing's disease) from 2007 to 2011. Burton T, et al. *Pituitary*. 2016;19:167-174.

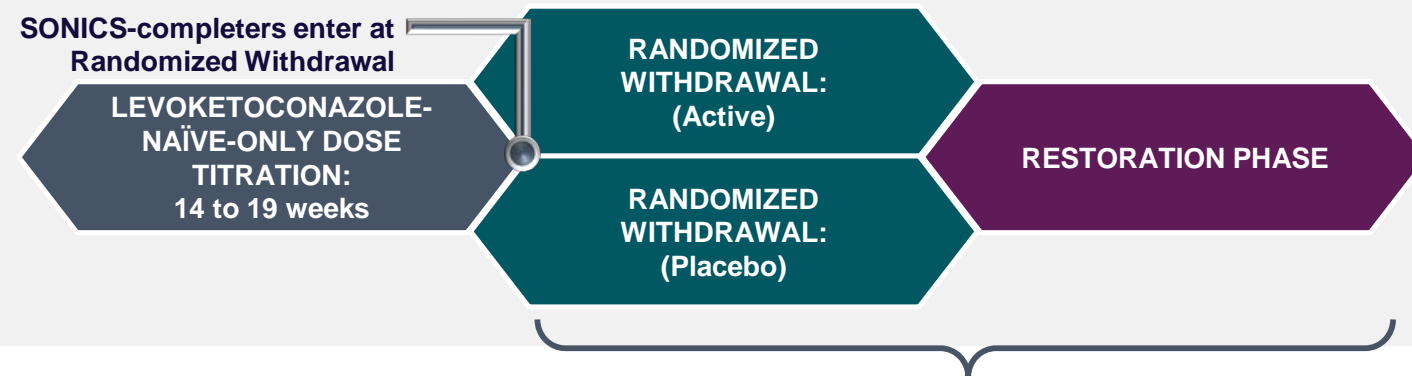
# Phase 3 Cushing's syndrome clinical program

## sonics™ 94 Patients Enrolled



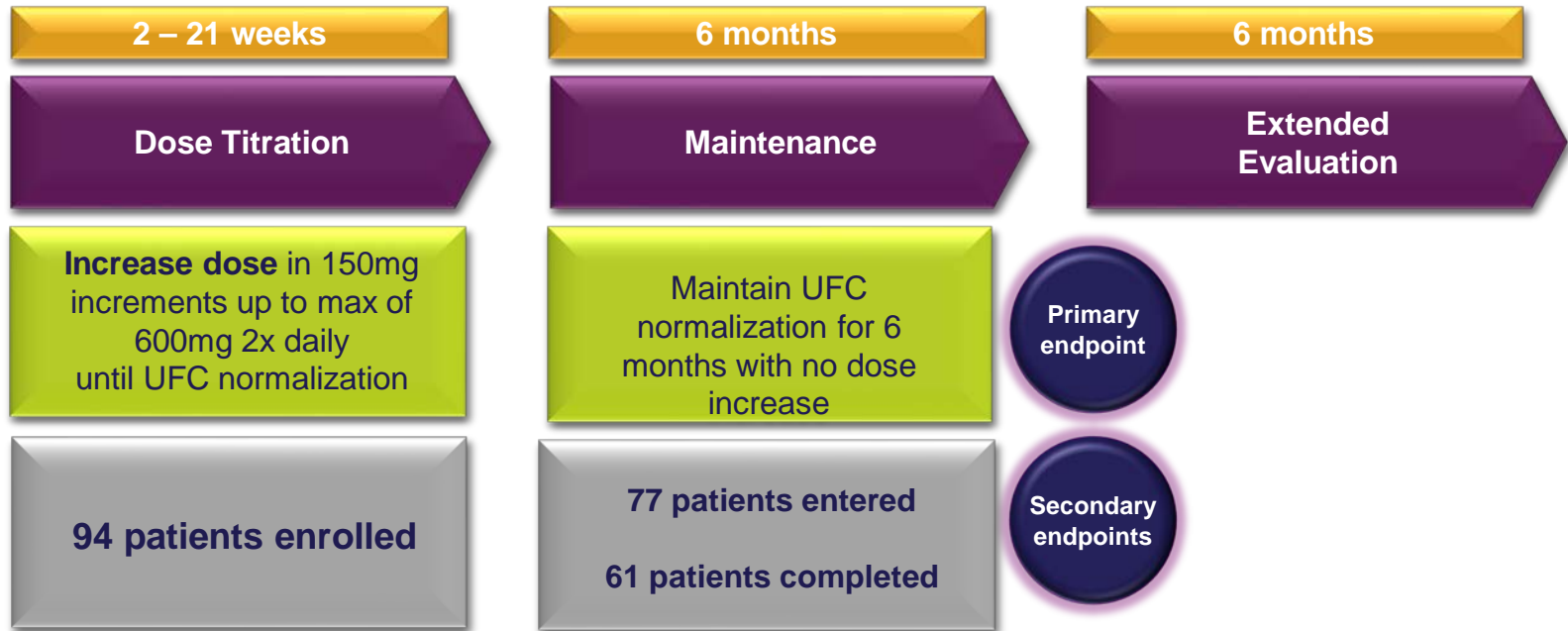
Both are pivotal trials to support FDA regulatory submission for approval

## LOGICS Target 35 Patients



\* OPTICS is not intended as pivotal trial.

# SONICS Study Design: Single Arm, Open-Label Phase 3

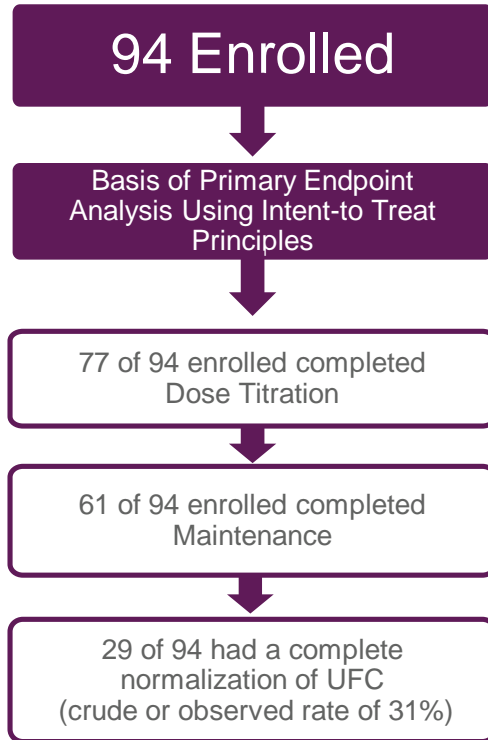




# SONICS Patient Demographics

	(N=94)
Age, years (mean, range)	44 (18-75)
Female (%)	82% (49% of childbearing potential)
BMI, kg/m <sup>2</sup> (median)	29
Pituitary source of Hypercortisolism	85%
Diagnosis of Diabetes	38%
Diagnosis of Hypertension	71%
Diagnosis of Hypercholesterolemia	36%
Baseline UFC (multiple of ULN)	Median 2.96, Mean 4.86

# SONICS Pre-specified Primary Endpoint Analysis (intention-to-treat)



- Sample size of 90 subjects was based on excluding a 20% or lower UFC response with 95% confidence (i.e. the lower limit of the 95% confidence interval would exceed 20%). Study enrolled 94.
- Results based on all 94 enrolled subjects, as pre-specified and per general FDA statistical guidance, used a mixed model repeated measures analysis, adjusting for covariates:

**UFC normalization in 30%, 95% CI: 21%, 40%; p<.025**

# UFC Responder Analysis At End Of Maintenance Phase

	N=94
<b>Primary endpoint of UFC normalization</b>	<b>30%, CI: 21%, 40% p&lt;.025*</b>
Sensitivity analysis of the primary endpoint (UFC normalization regardless of dose increase)	38%, CI: 28%, 49%
≥50% UFC decrease or normalization, regardless of dose increase	48%, CI: 37%, 58%
Maintenance completers with UFC data had ≥50% UFC reduction from baseline	76% (42/55) **

Analysis based on repeated measures model. Least squares mean estimate and associated 95% confidence interval  
 CI: 95% Confidence interval around the least squares means estimate from repeated measures model

\*1-sided vs. null hypothesis of 20% or lower rate

\*\*Data based on 55 maintenance phase completers with both baseline and month 6 UFC data available

# SONICS Key Secondary Endpoints at Month 6

Outcome Measure at End of Maintenance Phase	Adjusted* p-value of reductions from Baseline
Fasting Blood Glucose	<0.0001
Hemoglobin A1c	<0.0001
Total cholesterol	<0.0001
LDL-cholesterol	<0.0001
Body Weight	<0.0001
Body Mass Index	<0.0001

\*Hochberg adjustment applied to p-values to control type 1 error (except Body Mass Index); reductions from baseline based on least squares mean changes from repeated measures model.

No significant changes observed in blood pressure or c-reactive protein; small but statistically significant decrease observed in HDL-c

# SONICS Liver-Related Lab Values

Liver-Related Findings	N=94
Liver-related AEs defined in protocol as AE of special interest	7.4%*
ALT >3X ULN (includes those > 5x ULN)	10.6%
ALT >5x ULN	3.2%
Total bilirubin values > 1.5x ULN	0%

\*No severe drug-induced liver injury; no Hy's law; no transaminases >20x ULN; no obvious dose relationship (exposure relationships analyses pending)

## Most common reported AEs ( $\geq 15\%$ , both phases combined)

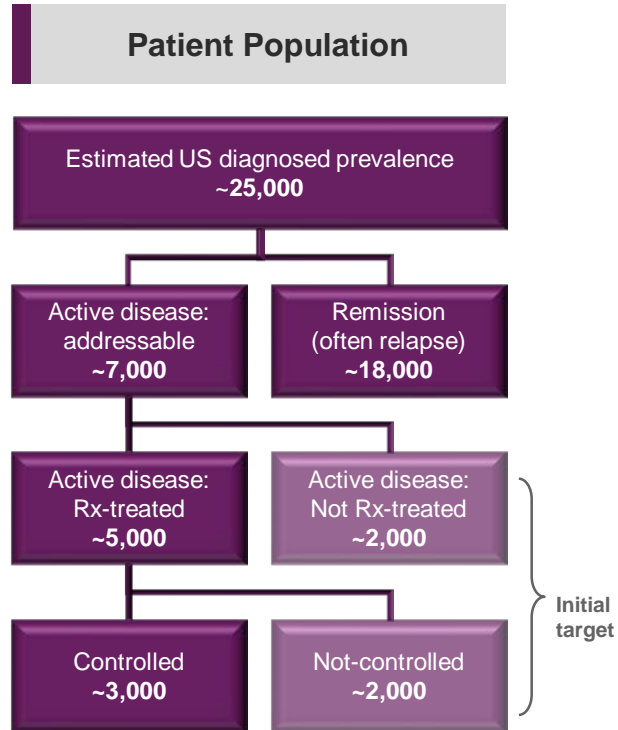
Adverse Event	Subjects $\geq 1$ AE	% of enrolled (N=94)
Nausea	30	32%
Headache	26	28%
Peripheral edema	18	19%
Hypertension	16	17%
Fatigue	15	16%
Diarrhea	14	15%
ALT increased*	14	15%

\*Includes all alanine aminotransferase (ALT) increases reported as an adverse event regardless of level or relationship to drug. A subset of these ALT increased events was also reported as adverse events of special interest.

# Recorlev Next Steps

- Strongbridge intends to discuss accelerated approval and the regulatory pathway with the FDA
- Report one year safety and efficacy data from SONICS (Q1 2019)
- Complete enrollment and report results (Q1 2019) from Phase 3 randomized withdrawal LOGICS study

# Recorlev U.S. Commercial Opportunity



- If approved, position Recorlev as first-line, first-choice therapy
- Based on SONICS data, Recorlev launch strategy could also include targeting off-label ketoconazole switches (~2,000-3,000 patients)
- Targeted pricing corridor of ~\$200K-\$400K per patient per year
- Recorlev time to peak sales could be pulled forward due to Macrilen strategic fit



# Macrilen

(macimorelin)

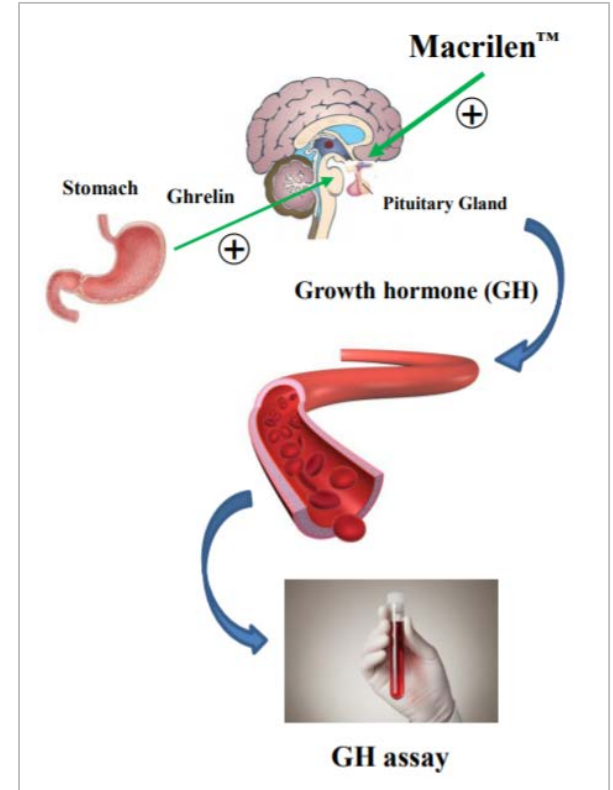
The first and only FDA-approved oral drug for  
diagnosing adult growth hormone deficiency

# Macrilen

Macrilen is an oral ghrelin receptor agonist (secretagogue) administered to stimulate growth hormone production

FDA approval in December 2017 for use in the diagnosis of patients with AGHD

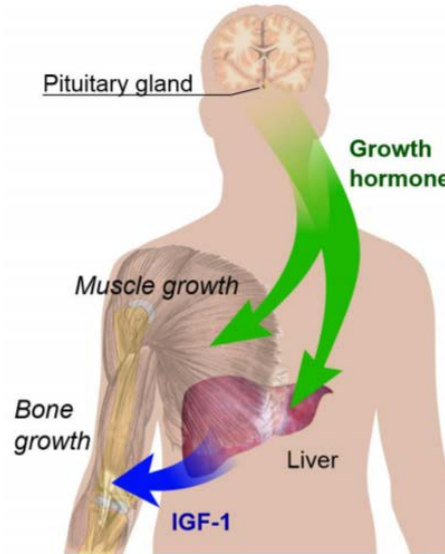
Strongbridge acquired U.S. and Canadian rights in January 2018 and launched Macrilen in the United States in July 2018



# Adult growth hormone deficiency (AGHD)

## Symptoms

- **Body composition altered:**
  - Increased fat mass
  - Decreased lean body mass
  - Reduced skeletal muscle strength
- **Cardiovascular (CV) issues:**
  - Increased risk of CV death
  - Abnormal lipids, other risk markers
- **Bone mineral density:**
  - Increased fracture rate
- **Overall:**
  - Decrease quality of life
  - Low physical/mental energy



Häggeström, Mikael.  
"Medical gallery of Mikael Häggeström 2014". Wikiversity  
Journal of Medicine 1 (2).

## Causes

- Tumors
- Surgery
- Cranial radiation
- Infectious / inflammatory
- Trauma / vascular injury
- Childhood onset (idiopathic)

**Growth hormone treatment has been shown in clinical trials to improve health for adults with GHD**

# Many patients are not screened for AGHD due to the complexity, tolerability and safety issues of the current tests

← NOT FDA APPROVED →

Current tests	Insulin Tolerance Test (ITT)	Glucagon Stimulation Test (GST)
Procedure	IV <sup>1,2</sup>	IM <sup>1,2</sup>
Number of blood draws	6 <sup>1</sup>	9 <sup>1,2</sup>
Total time	2-3 hours <sup>2</sup>	Minimum 3-4 Hours <sup>1,2</sup>
Requires medical supervision	Yes <sup>1,2</sup>	Yes <sup>3</sup>
Adverse events	<ul style="list-style-type: none"> <li>• Neuroglycopenia<sup>1,2</sup></li> <li>• Seizures<sup>1,2</sup></li> <li>• Loss of consciousness<sup>1,2</sup></li> <li>• Severe hypoglycemia<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Nausea<sup>1,2</sup></li> <li>• Vomiting<sup>1,2</sup></li> <li>• Headache<sup>1,2</sup></li> <li>• Late hypoglycemia<sup>1,2</sup></li> </ul>

1. Yuen KCJ. South Dartmouth, MA; Endotext [Internet]. <https://www.ncbi.nlm.nih.gov/books/NBK395585/>. Accessed February 19, 2018.

2. Agrawal V, Garcia JM. The macimorelin-stimulated growth hormone test for adult growth hormone deficiency diagnosis. *Expert Rev Mol Diag.* 2014;14(6):647-654.

3. Leong KS, et al. *Clin Endocrinol.* 2001;54: 463-468.

4. Post-Traumatic Hypopituitarism – Who Should be Screened, When, and How, Mark Quinn and Amar Agha

# Macrilen: The 1st and only FDA-approved oral drug for diagnosing adult growth hormone deficiency (AGHD)

Preferred route of administration	✓	Oral (Macrilen) versus IV (ITT) and IM (GST)
Less time for patient and office	✓	Macrilen assessment takes on average 1.5 hours as compared to 3-4 hours for GST and 2 hours for ITT
Fewer blood draws	✓	4 for Macrilen versus 6 for ITT and 9 for GST
Better safety profile	✓	ITT has been shown to induce hypoglycemia and therefore requires direct physician oversight and proximity to a crash cart
Improved tolerability	✓	Macrilen had far fewer adverse events than ITT in the Phase III study
No contraindications	✓	None in the label for Macrilen
Greater evaluability	✓	Macrilen showed improved evaluability compared to ITT
FDA-approved	✓	ITT and GST are not FDA-approved

# Macrilen accurately diagnoses AGHD: comparison to ITT

Results from an open-label, ITT-controlled, 2-way , randomized crossover study

Insulin Tolerance Test (ITT)  
(GH cutoff 5.1 ng/mL)

		Positive	Negative	Total Tests
Macrilen (GH cutoff 2.8 ng/mL)	Positive	55	4	59
	Negative	19	62	81
	Total	74	66	140

<b>AGREEMENT</b>	<b>74%*</b>	<b>94%*</b>	<b>84%</b>
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- Positive agreement higher (89%) for high-risk AGHD category
- Negative agreement 86-94%
- Labeling reflective of overall and risk-stratified agreements
- <1% of Macrilen tests were not evaluable vs. 17% of ITTs
- Macrilen was highly reproducible (91%) in the same patient

Negative Agreement: 93.94% (CI: 85.20%, 98.32%)- Met pre-defined performance criterion (i.e. excluded negative agreement with ITT of less than 75% with 95% confidence), Positive Agreement: 74.32% (CI: 62.84%, 83.78%)- Did not meet pre-defined performance criterion (i.e. could not exclude positive agreement with ITT of less than 70% with 95% confidence)

\* Co-Primary efficacy endpoints; a positive test is one that fails to reach the respective test's GH cutoff

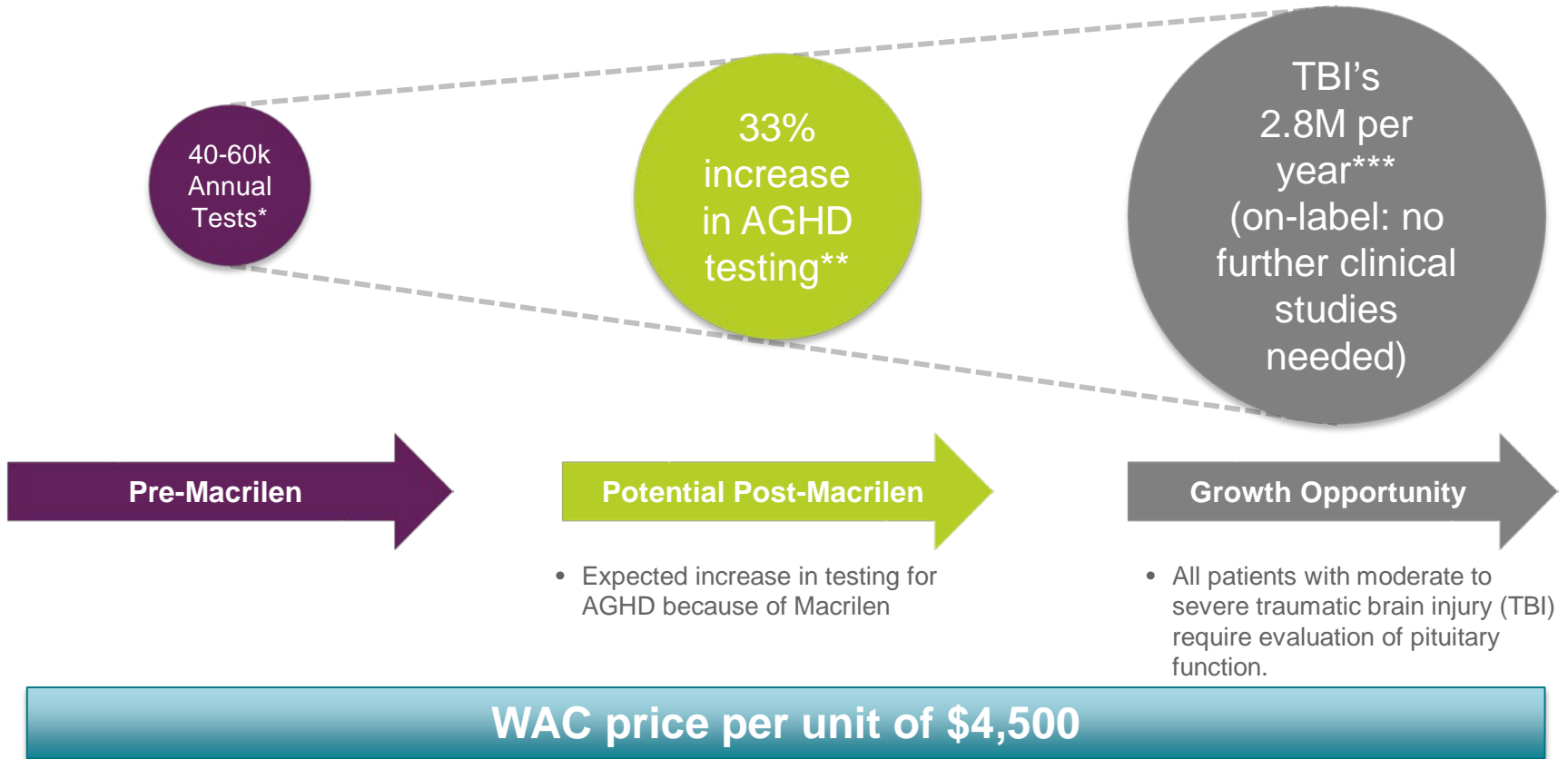
# Macrilen Safety Summary

- Macrilen well tolerated as compared to ITT (see table)
- Most common adverse reactions with Macrilen:
  - Dysgeusia (4.5%); dizziness, fatigue, and headache (3.9% each); nausea (3.2%)
  - Most adverse reactions were mild; none severe or led to failure to complete test
- QTc<sub>F</sub> upper 90% confidence limit about 11 ms at doses 2x-4x higher than used for GH stimulation (NO hERG inhibition)
  - Concomitant QT-prolonging drugs should be avoided
  - NO need to perform ECG before or after use of Macrilen
- DDI potential: Discontinue strong CYP3A4 inducers (avoids false-positive results)

GHST-emergent adverse events (TEAE)	Macimorelin (N=154)			ITT (N=157)		
	Frequency <sup>1</sup>	% <sup>2</sup>	N AEs <sup>3</sup>	Frequency <sup>1</sup>	% <sup>2</sup>	N AEs <sup>3</sup>
Any TEAE	39	25.3	77	151	96.2	761
Any likely or possible TEAE	22	14.3	37	149	94.9	710
Any <b>severe</b> TEAE	1	0.6	1	11	7	25

<sup>1</sup>: Number of subjects with any GHST-emergent AE, each subject was counted only once within each category  
<sup>2</sup>: Number of subjects with any AE / number of all subjects; <sup>3</sup>: Number of all AEs

# Macrilen Market Opportunity



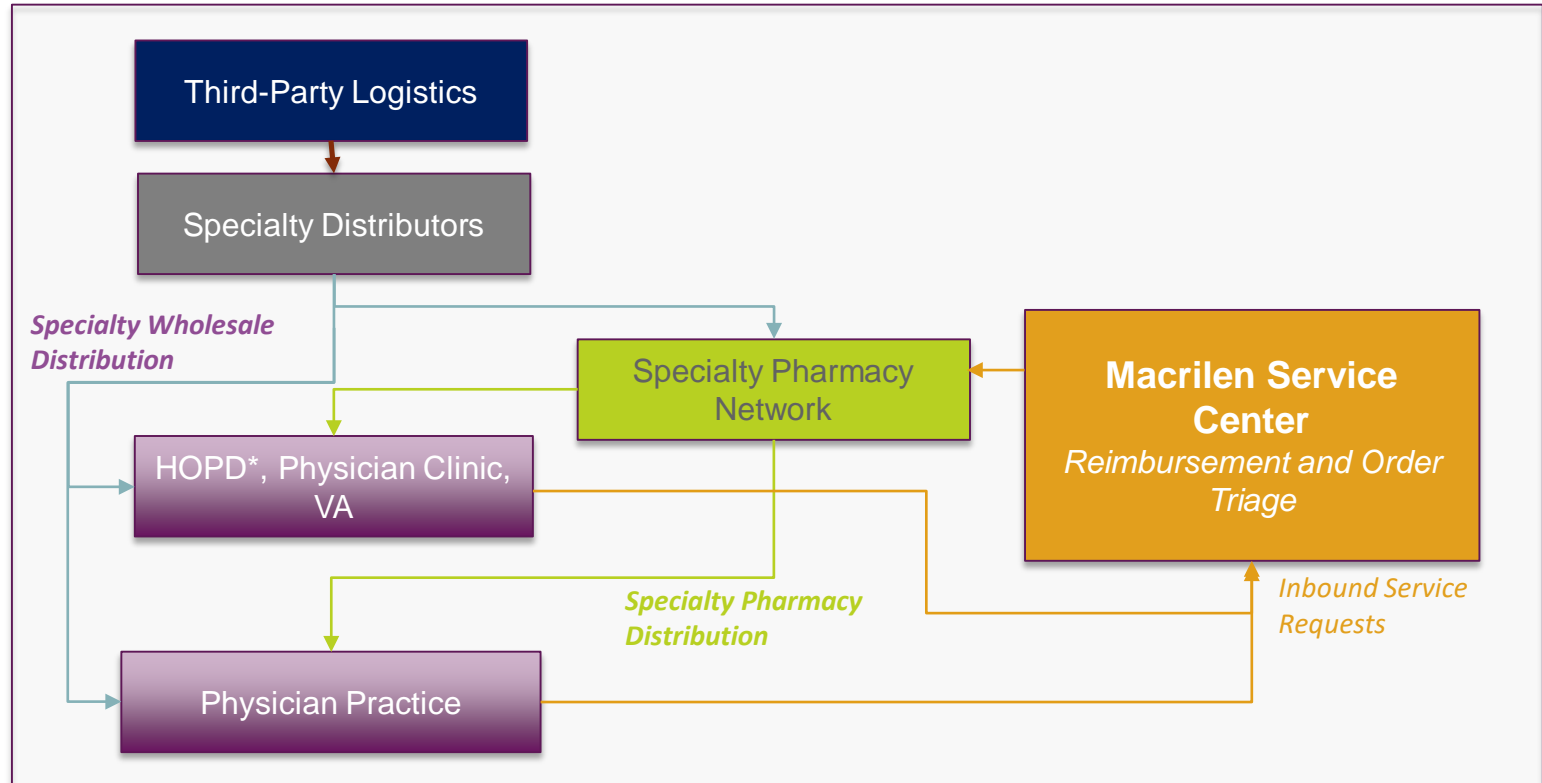
\*Oppenheimer 2011—manufacturer-sponsored research; Navigant, 2009—manufacturer-sponsored research; Symphony, 2017—manufacturer-sponsored research; TVG Research—manufacturer-sponsored research, 2017; Lumelian, 2017—manufacturer-sponsored research.

\*\*Results of quantitative (n=40 endocrinologists) and qualitative (n=5) market research conducted by a 3<sup>rd</sup> party sponsored by Strongbridge (2017).

\*\*\*<https://www.cdc.gov/traumaticbraininjury/severe.html>.



# Flexible and Scalable Distribution & Services Model



\*Hospital Outpatient Department

# Veldoreotide Extended Release

# Veldoreotide extended release: a novel, multi-receptor somatostatin analog

## BACKGROUND

Acquired immediate-release formulation of veldoreotide in 2015 and focused initial R&D on long-acting reformulation

10/2016: Successfully formulated for convenient, at-home, subcutaneous administration using PLGA microspheres

Formulation patent issued in U.S. for extended-release veldoreotide; patent protection to 2037

Data through Phase IIa: potential differentiated benefits from currently approved somatostatin analogues

Comparable maximal GH suppression to octreotide

Reduced impact on gallbladder function, bile acid production, and GI motility in rodents

Reduced impact on hormonal responses to mixed meals in healthy subjects

# Keveyis

(dichlorphenamide)

The first and only FDA-approved therapy  
for primary periodic paralysis\*

\* FDA-approved treatment for hyperkalemic, hypokalemic, and related variants of primary periodic paralysis

# Primary periodic paralysis: a spectrum of rare, chronic, genetic, neuromuscular disorders

## PPP

Causes recurrent, progressive, and debilitating episodes of muscle weakness and temporary paralysis<sup>2-4</sup>

~4-5k patients in the U.S.<sup>5</sup>

## Symptoms/triggers

Symptoms: clumsiness, extreme fatigue, weakness, palpitations, pain

Triggers: may include potassium, carbohydrates, rest after exercise, cold exposure, stress

## Impact of attacks

Paralytic attacks are acute episodes that can be debilitating<sup>4</sup>

Attacks may last from one hour to several days<sup>1</sup>

As patients age, muscle weakness can become permanent<sup>3</sup>

## Frequency

59% have weekly attacks

28% have daily attacks

# Keveyis revenue

**Q2 2018**  
actual

\$4.3m

**FY 2018**  
guidance

\$18-20m

# About Strongbridge

# The management team is highly experienced in managing orphan and ultra-rare disease assets

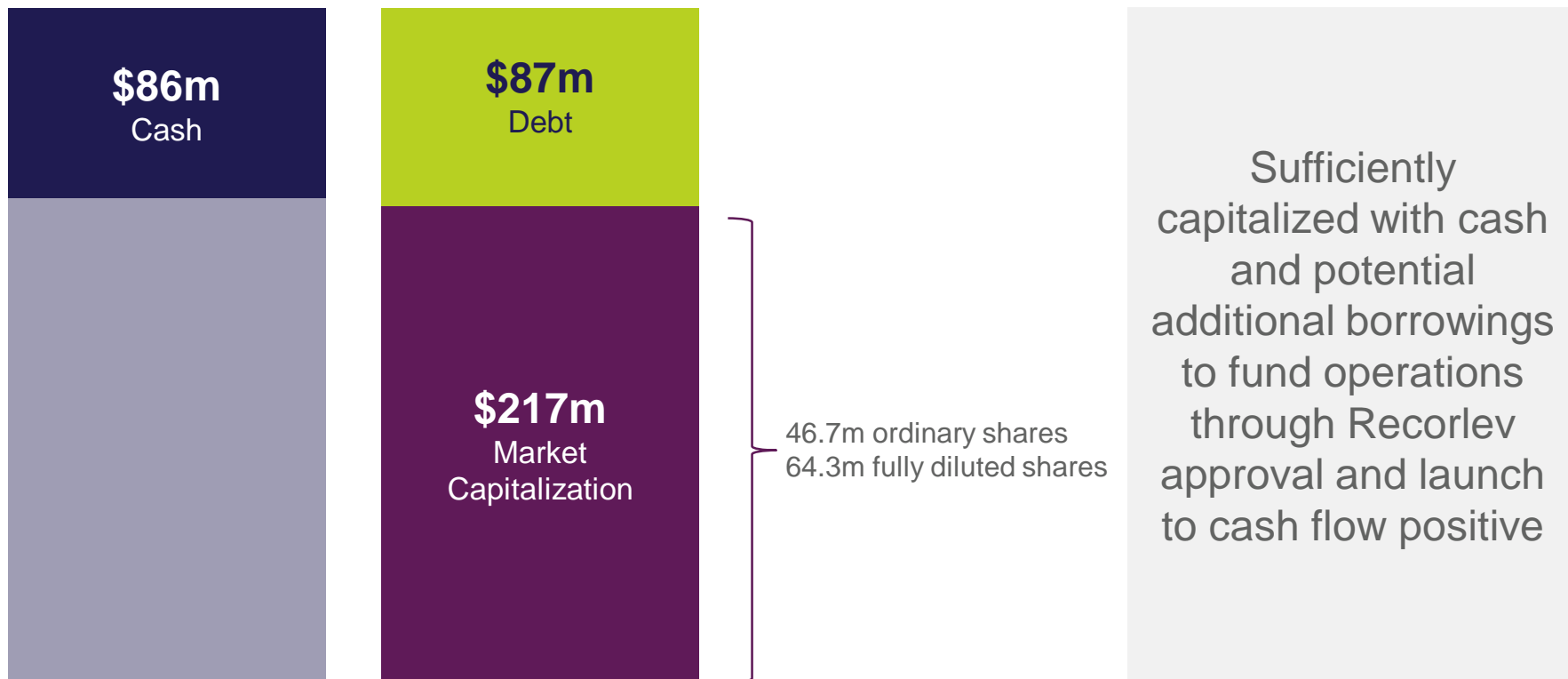
<p><b>Matthew Pauls</b> President, CEO, Director</p>	
<p><b>Fred Cohen, M.D.</b> Chief Medical Officer</p>	
<p><b>Brian Davis</b> Chief Financial Officer</p>	
<p><b>Stephen Long</b> Chief Legal Officer</p>	
<p><b>Robert Lutz</b> Chief Business Officer</p>	
<p><b>Dave Bonnell</b> SVP Sales &amp; Marketing</p>	
<p><b>Peter Valentinsson</b> SVP, Global Technical Operations</p>	
<p><b>Scott L. Wilhoit</b> SVP, Global Market Access &amp; Patient Services</p>	



# Intellectual property and orphan exclusivity

	IP		Orphan exclusivity	
	US	EU	US	EU
Macrilen	<p>2022 Composition of Matter</p> <p>2027 Method of use</p>	US and Canadian rights only	Dec 2024	US and Canadian rights only
Recorlev	<p>2030 Method of use: reducing CRP levels and systemic inflammation</p> <p>2026 Method of use: treating Cushing's syndrome</p>	2026 Method of use: treating Cushing's syndrome	7 years	10 years
Veldoreotide	2037 Formulation	Filed patent application for novel formulation	7 years	10 years
Keveyis	Exploring options	US rights only	Aug 2022	US rights only

# Strong Balance Sheet to Support Growth Objectives



Cash, debt and shares as of June 30, 2018. Market capitalization as of September 27, 2018

# Strongbridge Biopharma plc