

# Strongbridge Biopharma plc

March 2019

# 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, potential advantages of a product or product candidate, discussion with regulators regarding the regulatory approval process for RECORLEV, the release of additional planned analyses of the SONICS study, 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.

# Investment highlights

## Revenue-Generating Rare Disease Company

### Rare Endocrinology

**Macrilen** – recently sold rights to Novo Nordisk for \$145M plus tiered royalties; Novo funding commercial endocrine field force for three years

**Recorlev** – Recent results from pivotal Phase 3 SONICS trial for Cushing’s syndrome; met primary endpoint at 6 months and favorable benefit-risk profile through 12 months

**veldoreotide** – preclinical reformulation of differentiated somatostatin analog, fully owned

### Rare Neuromuscular

**Keveyis** – Only FDA-approved drug for all variants of Primary Periodic Paralysis

## Established Commercial Infrastructure

Fully integrated commercial operations in two rare disease therapeutic areas



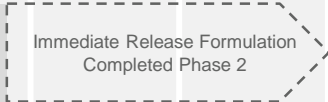


## Effective Business Development

Proven ability to identify, evaluate and transact efficiently and effectively

## Well Capitalized

- ~\$122M in cash; no debt (as of 12/31/2018)

# Strongbridge and partnered product pipeline

		Indication/ Target Disease	Pre- clinical	Phase 1	Phase 2	Phase 3	Marketed	Commercial Lead
Rare Endocrinology	<b>MACRILEN™</b> (macimorelen)	Adult Growth Hormone Deficiency diagnosis	Marketed					 US and Canada
	<b>RECORLEV™</b> (levoketoconazole)	Endogenous Cushing's syndrome	Phase 3					 Global
	<b>veldoreotide modified-release</b>	Acromegaly, other conditions modifiable through activation of somatostatin receptors, such as Cushing's disease and neuroendocrine tumors	Pre-clinical	 Immediate Release Formulation Completed Phase 2				 Global
Rare Neuro-muscular	<b>KEVEYIS®</b> (dichlorphenamide)	Primary Periodic Paralysis	Marketed					 US

# Potential value drivers in 2019

## Recorlev

- FDA Type C meeting (Q1 2019)
- LOGICS topline data (Q4 2019)
- SONICS data presentations (through H1 2019)

## Keveyis

- Grow revenue-- continue to organize and construct the market
- Focus commercial investment
- Pursue life cycle opportunities to extend exclusivity runway beyond 2022

## Macrilen

- Execute seamless transition of Macrilen to Novo Nordisk
- Maximize Strongbridge royalty income by collaborating commercially to accelerate growth

## Corporate

- Evaluate additional late-stage or commercial rare disease assets

# Macrilen

(macimorelin)

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

# Strategic rare endocrine transaction and collaboration with Novo Nordisk

DEAL TERMS	
<b>Upfront Cash Payment</b>	\$145 million from Novo Nordisk for U.S. and Canadian rights to Macrilen
<b>Royalty</b>	Strongbridge will receive tiered royalties related to sales of Macrilen through 2027: <ul style="list-style-type: none"><li>• 2019-2021: 12% of annual net sales</li><li>• 2022-2027: 4% of annual net sales up to \$100M plus 8% of net sales over \$100M</li></ul>
<b>Strongbridge Endocrine Field Force</b>	Novo Nordisk will leverage and fund Strongbridge's 23-person rare endocrine commercial field organization for up to three years (approximately \$7-\$8 million per year)
<b>Equity Investment</b>	Novo Nordisk purchased 5.2 million ordinary shares at a purchase price of \$7.00 per share

# Recorlev

(levoketoconazole)



# Cushing's syndrome complications and comorbidities

## Cushing's syndrome symptoms



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



## Unmet need and burden of illness

Per a 2017 study\* of 224 patients, cortisol control was not achieved with any treatment modality—including surgery, radiation and medicines—in more than half of the subjects:

- » 49.1% control achieved
- » 29.9% control not achieved
- » 21.0% indeterminate

Cushing's disease 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

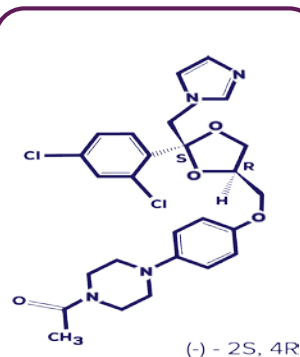
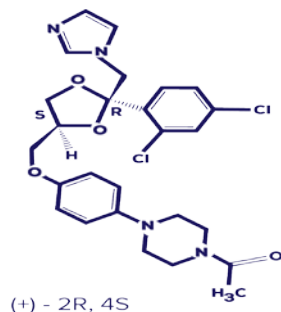
Source: Company sponsored research and published research including Feelders RA, Hofland LJ. (J Clin Endoc Metab. 2013;98(2):425-438) and Daly et al. (J Clin Endoc Metab 2006) \*According to a retrospective analysis of claims from a large US commercial health plan (885 selected Cushing's disease cases and 2,655 matched controls without Cushing's disease) from 2007 to 2011. Burton T, et al. *Pituitary*. 2016;19:167–174. Geer et. al. (Endoc Pract 2017 Aug;23(8):962-970)

# Recorlev (levoketoconazole) is the pure 2S,4R enantiomer of ketoconazole

## KETOCONAZOLE

Two enantiomers combined

Not approved in the US to treat Cushing's syndrome



## RECORLEV

Single enantiomer only (new chemical entity)

Single enantiomers often have significantly different clinical effects than their racemates

US/EU orphan designation for Cushing's syndrome

## Development History and Regulatory Pathway

- Global phase 3 development program for Cushing's syndrome – SONICS topline results positive
  - Previously studied in two Phase 2 studies of diabetes (118 subjects received Recorlev)
- FDA 505(b)(2) regulatory approval pathway
  - Differentiated FDA 505(b)(2) drugs de-risk approval and have been successful in rare diseases (e.g., Korlym, Procysbi)

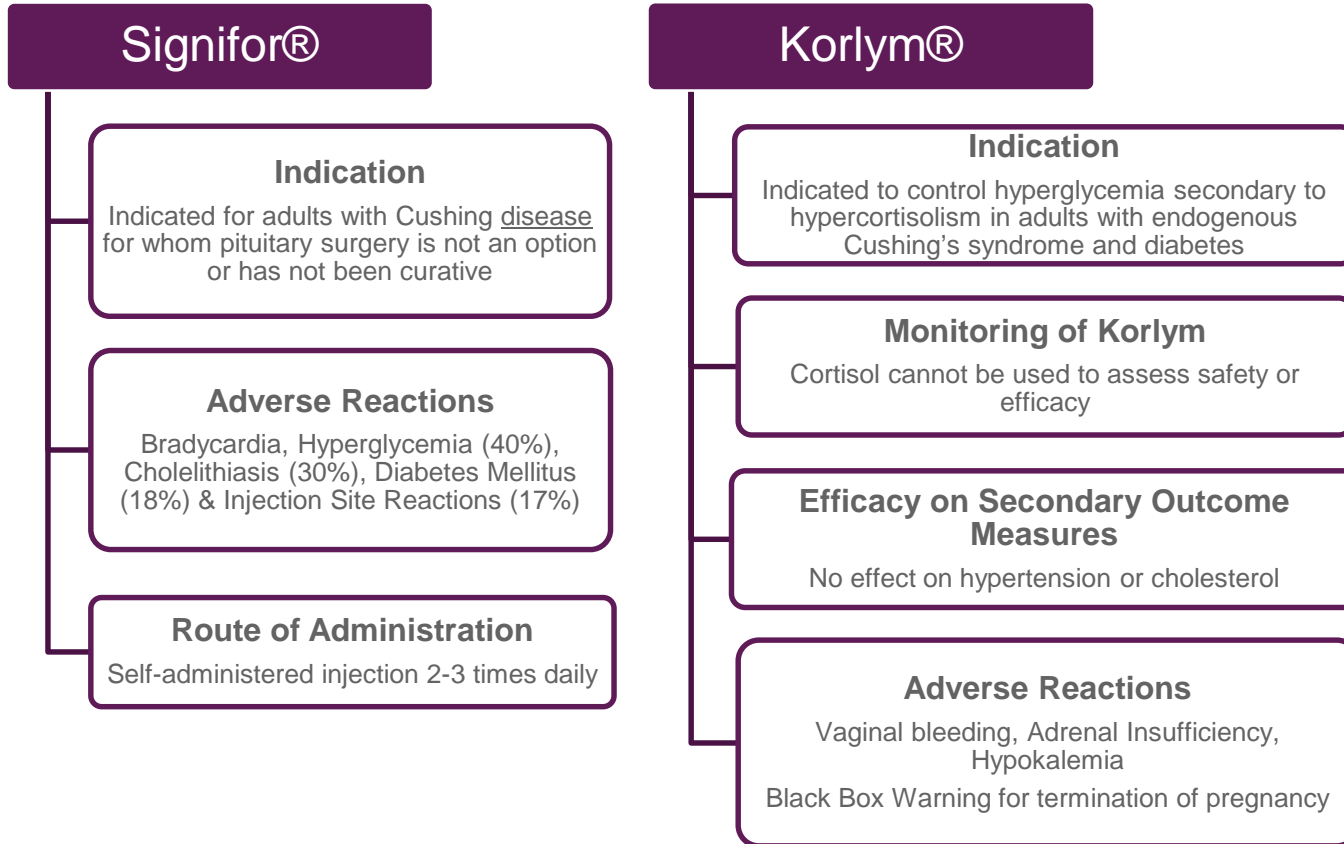
# Ketoconazole labeled as last-line antifungal in U.S.

## Includes warning against off label use in prostate cancer and Cushing's syndrome

<b>Indications</b>	Last-line anti-fungal, not indicated for Cushing's syndrome	Ketoconazole Tablets should be used only when other effective antifungal therapy is not available or tolerated...Ketoconazole Tablets are indicated for the treatment of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies...." <sup>1</sup>
<b>Dosage and administration</b>	Limited 6-month course, 400-mg max dose, 200-mg strength, once daily	"The recommended starting dose of Ketoconazole Tablets is a single daily administration of 200 mg (one tablet). If clinical responsiveness is insufficient within the expected time, the dose of Ketoconazole Tablets may be increased to 400 mg (two tablets) once daily.... The usual duration of therapy for systemic infection is 6 months." <sup>1</sup>
<b>Boxed warnings</b>	Hepatotoxicity; QT prolongation and drug interactions leading to QT prolongation	ALT Monitoring: "During the course of treatment, serum ALT should be monitored weekly for the duration of treatment. If ALT values increase to a level above the upper limit of normal or 30 percent above baseline, or if the patient develops symptoms, ketoconazole treatment should be interrupted." <sup>1</sup>
<b>Adverse reactions to unapproved uses</b>	FDA admonition of off-label use	"Ketoconazole has been used in high doses for the treatment of advanced prostate cancer and for Cushing's syndrome when other treatment options have failed. The safety and effectiveness of ketoconazole have not been established in these settings and the use of ketoconazole for these indications is not approved by FDA." <sup>1</sup>

1. Excerpted from Teva Pharmaceuticals USA, Inc. Ketoconazole Tablets U.S. Prescribing Information 2015

# Significant unmet need in Cushing's disease/syndrome



# Phase 3 Recorlev clinical program



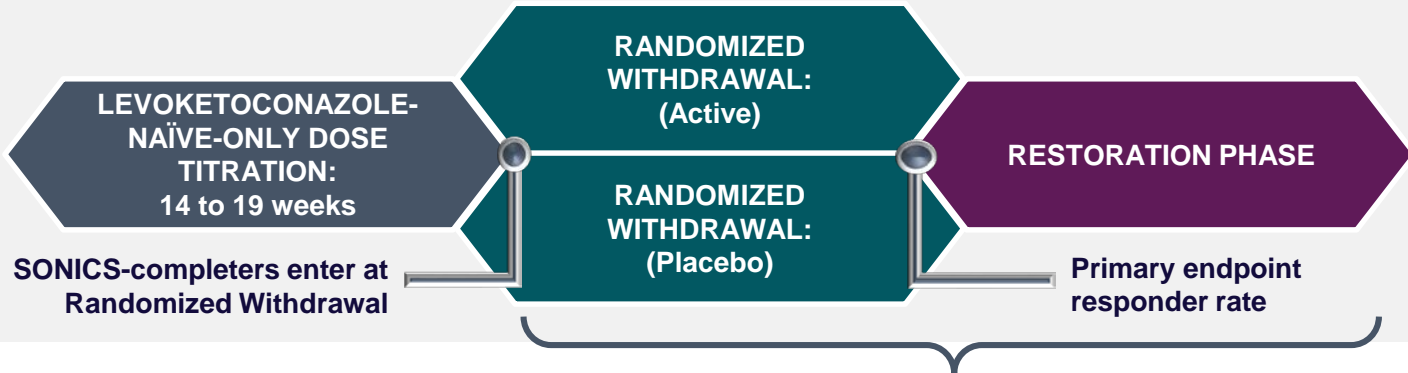
Open label; 94 patients enrolled



Both are pivotal trials to support FDA regulatory submission for approval



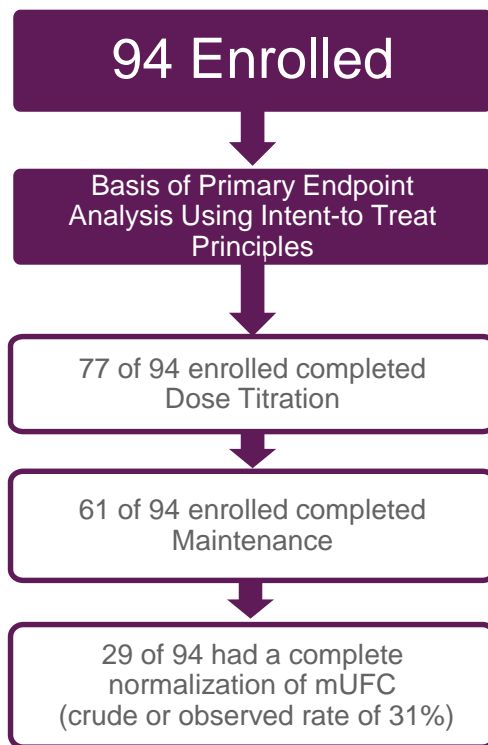
Randomized withdrawal; 54 randomized patient target



\* OPTICS is not intended as pivotal trial

Up to 19 weeks

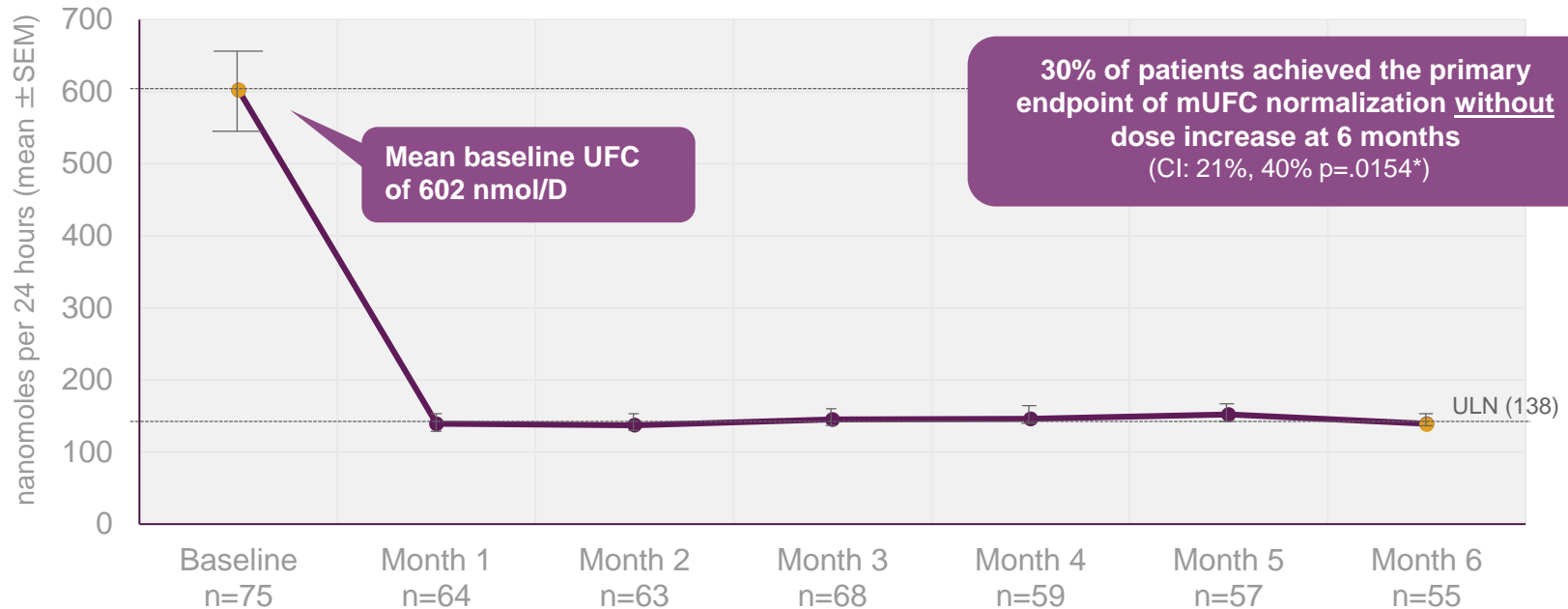
# SONICS - Summary of Maintenance Phase Results



- **Primary endpoint achieved statistical significance**  
30% of patients achieved mUFC normalization without dose increase (95% CI: 21%, 40%;  $p=.0154$ )
- **Six key cardiovascular secondary endpoints achieved statistical significance** ( $p<.0001$  for all)
- **Liver enzyme elevations**  
11% of patients had liver enzyme elevation  $>3x$  ULN on or before day 60 of maintenance; all reversible upon discontinuation without clinical sequelae
- **No unexpected safety signals**  
13% discontinuation rate due to treatment-emergent adverse events

# SONICS trial achieved primary endpoint

## Sustained reduction in mean UFC for six months after dose titration



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

# mUFC responder analysis at end of maintenance phase

	N=94
<b>Primary endpoint of mUFC normalization <u>without</u> dose increase</b>	30%*, CI: 21%, 40% p=.0154
Maintenance completers with mUFC data and normalization or $\geq 50\%$ mUFC reduction from baseline	76% (42/55) **

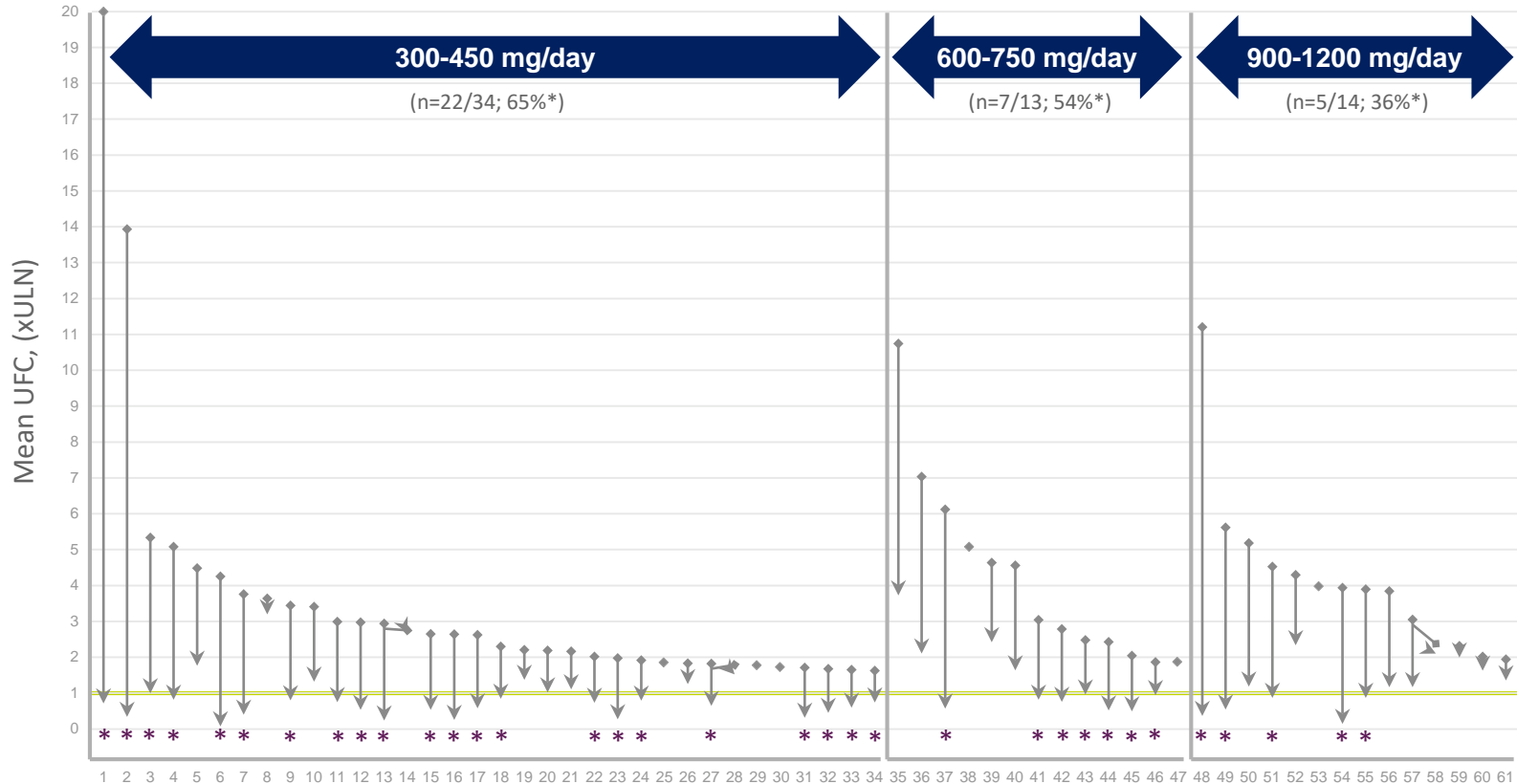
\* Analyses were based on mixed-effects, repeated measures model with an underlying binomial distribution and a logit link function and adjusting for baseline covariates. Estimates of the response and the associated the 95% Confidence Intervals (CIs) and the one-sided p-value (for the primary analysis only) are presented.

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



# mUFC response by patient for each patient who completed maintenance phase (n=61)

◆ Baseline  
▼ 6 months



\*Refers to proportion of subjects in each dose category achieving mUFC normalization in month 6 of maintenance phase regardless of need for dose increase.

# SONICS achieved statistical significance in key secondary endpoints

Outcome Measure at End of Maintenance Phase	Baseline Mean, (n)	Mean Change From Baseline <sup>†</sup> , (n)	Adjusted* p-value of reductions from Baseline
Fasting Blood Glucose	5.8 mmol/L, (76)	-0.7, (50)	<0.0001
Hemoglobin A1c	6.0%, (77)	-0.4, (55)	<0.0001
Total cholesterol	5.7 mmol/L, (77)	-1.1, (53)	<0.0001
LDL-cholesterol	3.3 mmol/L, (77)	-1.0, (53)	<0.0001
HDL-cholesterol	1.6 mmol/L, (77)	-0.2, (53)	<0.0001
Body Weight	82.1 kg, (77)	-5.1, (54)	<0.0001

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

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

# Liver safety findings in maintenance phase

	Recorlev	Signifor LAR*
ALT >3X ULN (includes those > 5x ULN)	10.6%	14%
ALT >5x ULN	3.2%	5%
Total bilirubin values > 1.5x ULN	0%	NA
Liver warning & precautions	TBD	Yes (but no black box)
	<p>SONICS Monitoring Protocol:</p> <p>At least once every two weeks during dose titration.</p> <p>Monitored monthly for six months after the therapeutic dose is established; then every three months thereafter.</p>	<p>Product Labeling:</p> <p>No boxed warning for liver safety.</p> <p>Monitor at least once prior to treatment and again after the first two-to-three weeks of treatment; then monthly for three months.</p>

\* Signifor LAR Prescribing Information

# Most commonly 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.

## Adverse Events of Special Interest

Liver-related (7%)

QTc prolongation (5%)

Adrenal insufficiency (3%)

# SONICS extended evaluation phase

- 6-month treatment phase after 6-month maintenance phase
  - 60 of 61 patients who completed the maintenance phase elected to participate in the extended evaluation phase
    - 46 patients completed the extended evaluation phase (comparable discontinuation rate to the dose titration and maintenance phases)
- Key protocol differences in extended evaluation phase compared to maintenance phase included:
  - Investigators instructed to alter daily dose as needed in extended evaluation to maintain cortisol control and manage side effects
  - Clinical visits every three months (compared to monthly in maintenance phase)
- Extended evaluation phase meets objective of showing positive long-term benefit-risk profile of Recorlev

# SONICS extended evaluation phase top-line results

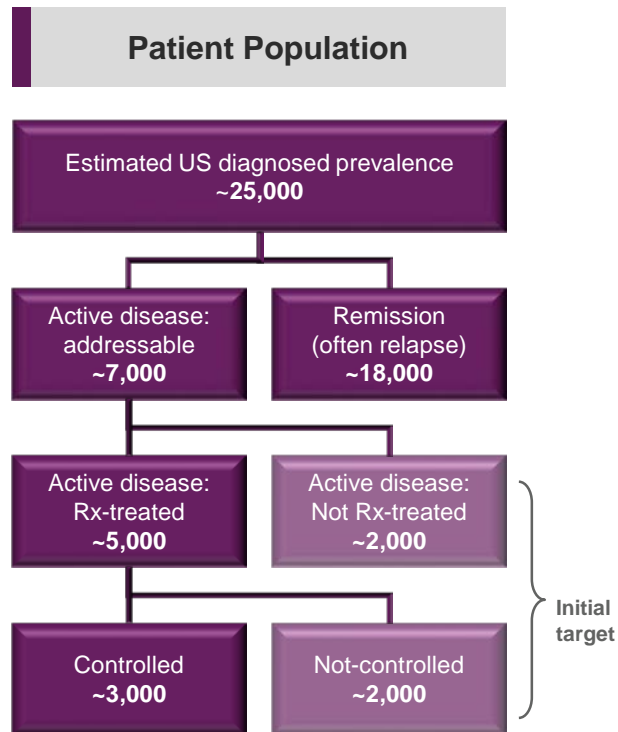
## No new drug-related safety signals

- Four patients (6.7%) discontinued during extended evaluation phase due to adverse events
- No patients experienced an increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of greater than three times the upper limit of normal
  - No Adverse Events of Special Interest (AESI) related to liver injury or dysfunction
- Treatment-Emergent Adverse Events (TEAEs)  $\geq 5\%$ :
  - Arthralgia (7%), QTc prolongation (7%), headache (7%), hypokalemia (7%), and nasopharyngitis (5%)
    - QTc prolongation greater than 460 msec was not observed in the extended evaluation phase
  - Nausea (2%) and headache (7%) were reported at lower rates as compared to the previously reported aggregate rates of 32% (nausea) and 28% (headache) from the dose titration and maintenance phases

# SONICS extended evaluation phase top-line efficacy results

- An observed-case analysis of completers was used to evaluate mUFC responders
- At the end of the extended evaluation phase:
  - normalization of mUFC was observed in 41% of patients
  - normalization or at least 50% improvement in mUFC was observed in 68% of patients
- Clinically meaningful improvements in key cardiovascular risk markers were observed through the extended evaluation phase
  - Reductions from baseline in mean hemoglobin A1C, fasting glucose, and total and LDL-cholesterol
- Weight loss and reduction in body mass index (BMI) continued through the extended evaluation phase

# Recorlev U.S. Commercial Opportunity



- SONICS data may support Recorlev launch strategy of positioning for both:
  - Drug-naïve patients, as first-line drug treatment
  - Patients on other drugs, including approximately 2,000 off-label ketoconazole patients
- Recorlev profile supports pricing in the currently established Cushing's drug pricing corridor of ~\$200K-\$400K annually
  - Current FDA-approved drugs for Cushing's are not generally managed by payers – little-to-no requirement for a generic fail-first or step edit (including off-label ketoconazole)
- Ongoing Macrilen / endocrinology presence may accelerate Recorlev time to peak penetration



# Recorlev upcoming milestones

- Type C meeting to discuss NDA filing strategy by end of Q1 2019
- Additional SONICS data to be reported at upcoming medical meetings
  - Pituitary Society – March 20-22, 2019
  - Endocrine Society – March 23-26, 2019
  - AACE – April 24-28, 2019
- LOGICS top-line data expected Q4 2019

# 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>

## 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

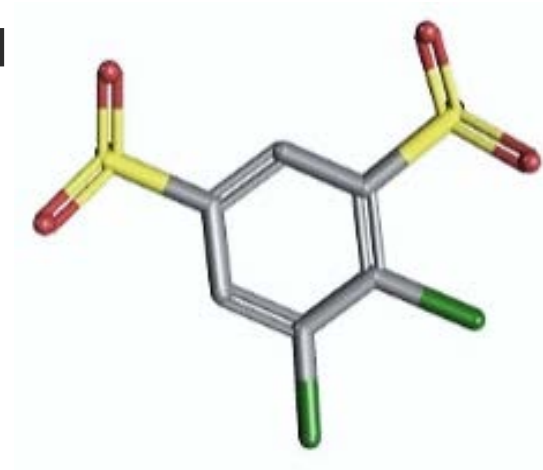
# Estimated 4,000 – 5,000 diagnosed U.S. patients



\* Based on Strongbridge analysis of medical claims database. Identified patients were required to have medical activity of any type in the last 12-36 months.

# Keveyis Overview

- Strongbridge acquired U.S. rights to Keveyis<sup>®</sup> (dichlorphenamide) in December 2016 and launched in April 2017
- Keveyis is the **first and only** FDA-approved therapy indicated for the treatment of:
  - Primary hyperkalemic periodic paralysis
  - Primary hypokalemic periodic paralysis
  - Related variants
- Twice-daily dosing in an oral tablet formulation
  - Starting dose is 50 mg 2X daily-- can be titrated up to 100 mg 2X daily



# Strategic priorities & revenue guidance

Continue to organize and construct the market

Focus commercial investment to accelerate pathway to profitability

Pursue life cycle opportunities to extend exclusivity runway beyond 2022

2018 revenues: \$16.8M  
2019 revenue guidance: \$18-20M

# 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

# Potential value drivers in 2019

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