ARVELLE THERAPEUTICS

JEFFERIES 2019 LONDON HEALTHCARE CONFERENCE

NOVEMBER 20, 2019

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ARVELLE THERAPEUTICS OVERVIEW

- Emerging biopharma bringing innovative solutions to patients suffering from CNS disorders
- Initial focus on commercializing cenobamate in Europe for treatment resistant epilepsy
- Cenobamate is a highly differentiated product with the potential to transform epilepsy treatment
- An NDA for cenobamate has been filed in the U.S. by SK Life Science[1] with PDUFA date Nov 21, 2019
- Arvelle plans to file the MAA in H1 2020 and launch as soon as H1 2021 after EMA approval and first market pricing approvals
- Arvelle has exclusive European rights to cenobamate and is building a world-class commercial organization based in Zug, Switzerland to support the European launch of cenobamate
- Arvelle is well-capitalized by a global syndicate that invested $207.5 million in its start-up financing

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LSP CONNECTING INVESTORS TO INVENTORS

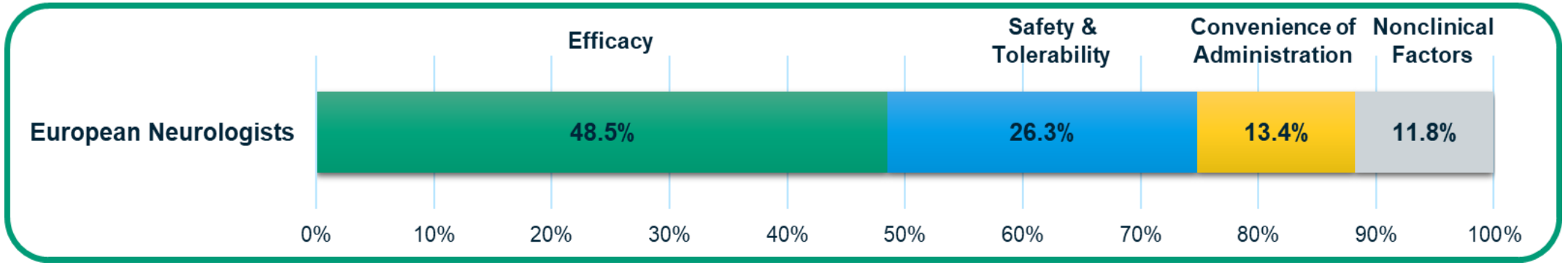
1. SK Life Science Inc., is the U.S. subsidiary of SK Biopharmaceuticals, an affiliate of the SK Group, Korea.

SIGNIFICANT UNMET NEED IN TREATMENT RESISTANT EPILEPSY

Key conclusions from European neurologists*

- Efficacy is the main driver of physician prescribing
- High level of unmet need for agents offering greater seizure-reduction
- Only moderate satisfaction with the efficacy of key AEDs
- Percentage of treatment resistant epilepsy patients has remained unchanged at 30-40+% despite introduction of new AEDs

*"**Seizure freedom** is the ultimate goal of epilepsy treatment, and an investigational anti-epilepsy drug with a **high seizure-freedom rate** in refractory patients would be **groundbreaking**"*



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*Source: Christmann, Bethany. "Epilepsy – Unmet Need – Detailed, Expanded Analysis – Treatment Refractory Epilepsy (Partial Onset) – US/EU." *Decision Resources Group.* May 2018: 5, 32, 47. AED: anti-epilepsy drug

INITIAL FOCUS ON LARGEST SEGMENT OF EPILEPSY MARKET: FOCAL AND GENERALIZED SEIZURES

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= 10,000 patients

Arvelle initial target population ~ 1 million patients in Europe still seizing despite treatment with two or more AEDs (treatment resistant)

Focal – Treatment Resistant Target Population

Generalized – Treatment Resistant Target Population

Arvelle will also eventually play in the orphan epilepsy market

ARVELLE THERAPEUTICS

GW pharmaceuticals ZOGENIX STOKE THERAPEUTICS

LGS + TSC + Dravet

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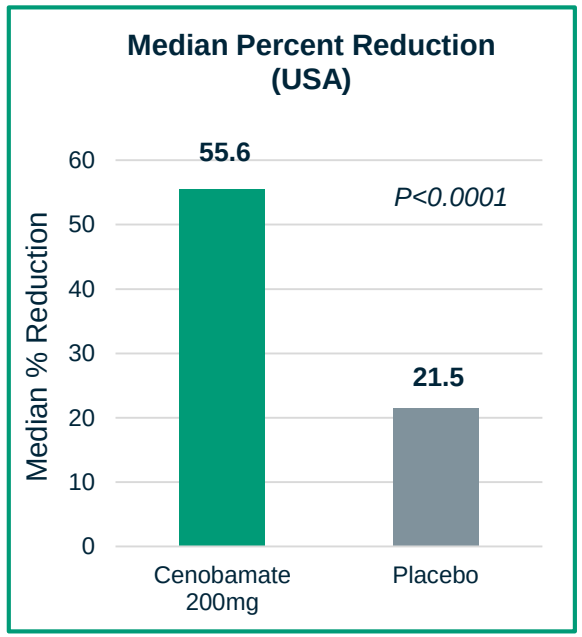
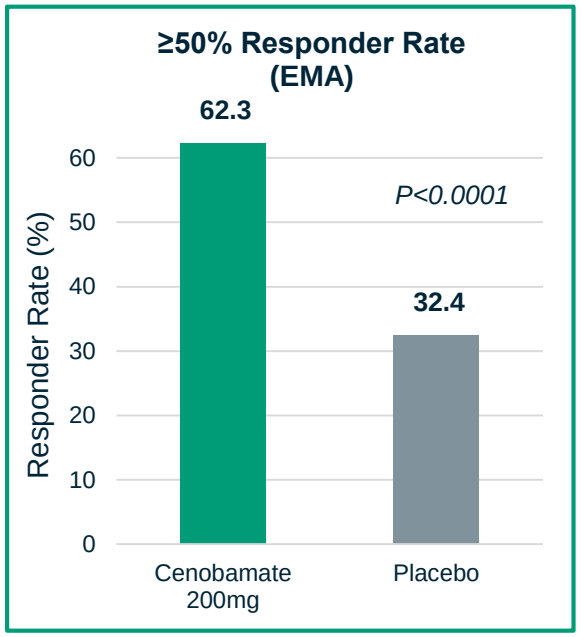
Sources: Global Data 2016, GW Pharma 10-K, Zogenix 10-K

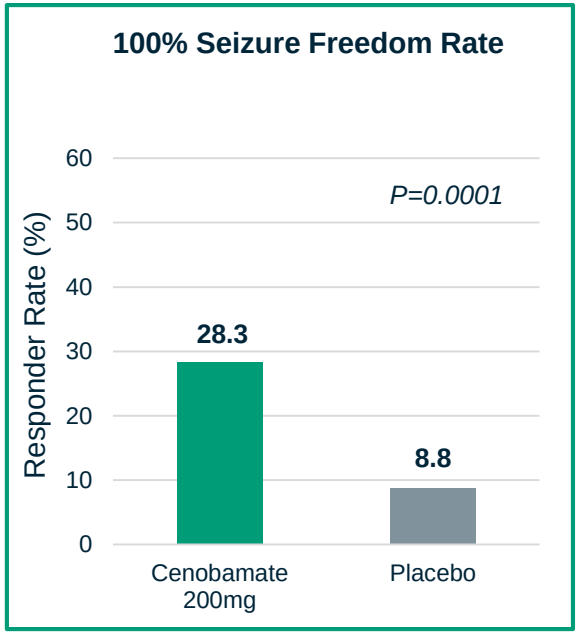
CENOBAMATE DEVELOPMENT OVERVIEW

- Dual mechanism of action pairs $GABA_A$ positive allosteric modulation with sodium channel block
- Once-a-day oral tablet with ~50-60 hour half-life
- >2500 clinical subjects have been exposed to cenobamate:
  - 22 Phase 1 studies (completed)
  - Three Phase 2 studies (completed)
  - One Phase 3 safety study (open label extension ongoing)
- Seizure freedom rates seen in Phase 2 studies exceed current standard of care
  - Study C013 (6wk maintenance): 28.3% seizure freedom vs. 8.8% pbo (200mg, p=0.0001)
  - Study C017 (12wk maintenance): 21.1% seizure freedom vs. 1.0% pbo (400mg, p<0.0001)
- NDA was filed by SK Life Science upon completion of the Phase 3 safety study (C021)
- Patent protection until 2031 with likely EU regulatory exclusivity until 2032

STUDY C013 : UNPRECEDENTED LEVELS OF EFFICACY AND SEIZURE FREEDOM RATES





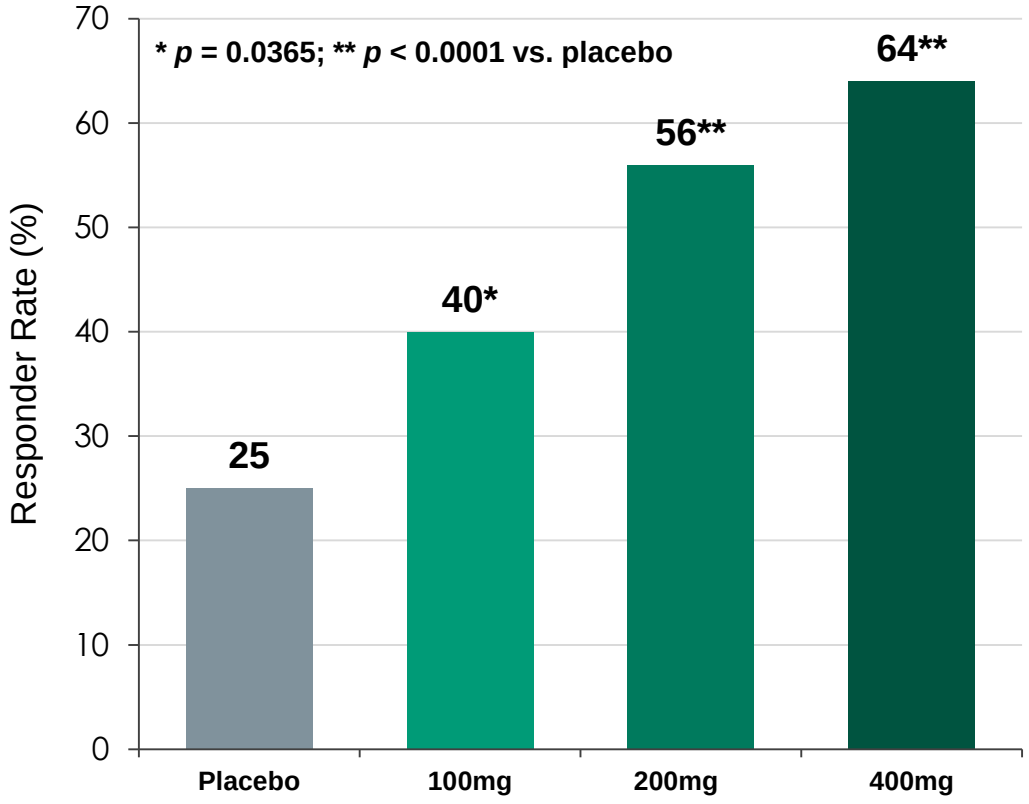


Consistent seizure reduction rates across the different regulatory endpoints and seizure freedom in patients with refractory partial-onset seizures

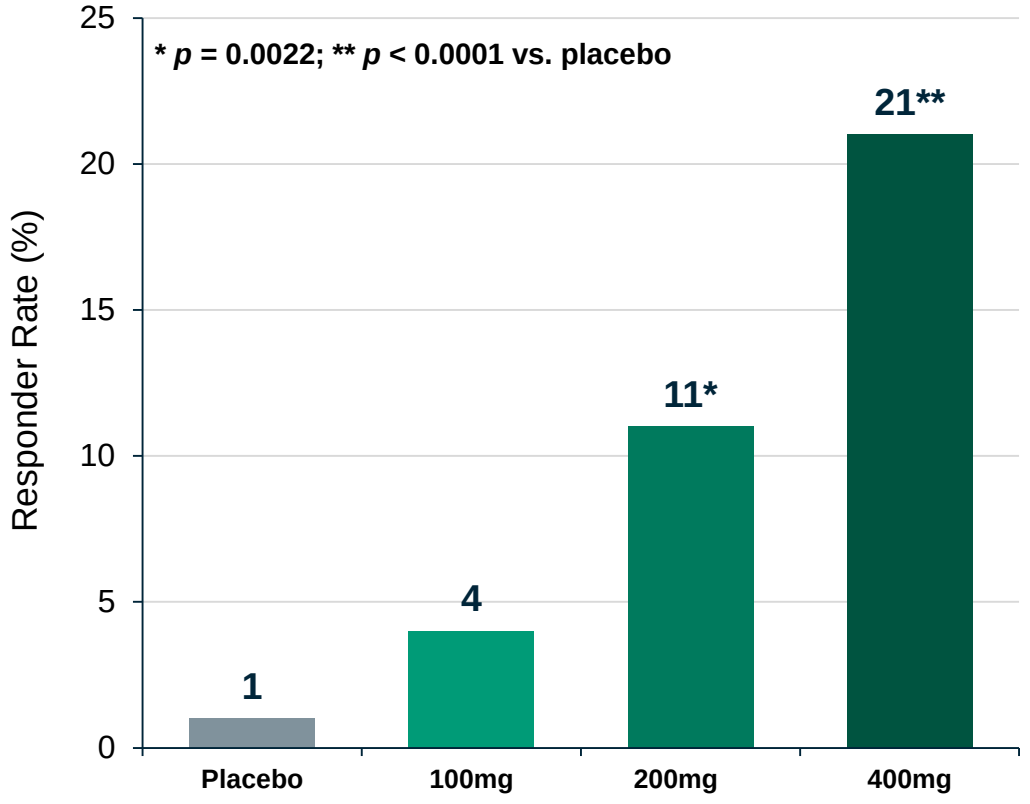
Source: Data on file, SK Life Sciences

STUDY C017: PRIMARY EFFICACY ENDPOINT FOR EMA AND SEIZURE FREEDOM RATES (100% RESPONDER)

≥50% Responder Rate
(12-week maintenance phase)



100% Responder Rate
(12-week maintenance phase)



ARVELLE THERAPEUTICS

Source:Krauss GL, *et al.*, Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. *Lancet Neurol.* 2019; (published online Nov 13)

STUDY C017 RECENTLY PUBLISHED ONLINE IN THE NOVEMBER EDITION OF *THE LANCET NEUROLOGY*

Articles

Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial

Gregory L. Krauss, Pavel Klein, Christian Brandt, Sang Kun Lee, Ivan Milanov, Maja Milovanovic, Bernhard J Steinhoff, Marc Kamin

Summary

Background More than a third of patients with epilepsy are treatment resistant, and thus new, more effective therapies to achieve seizure freedom are needed. Cenobamate (YKP3089), an investigational antiepileptic drug, has shown broad-spectrum anticonvulsant activity in preclinical studies and seizure models. We aimed to evaluate the safety, efficacy, and tolerability of adjunctive cenobamate in patients with uncontrolled focal (partial)-onset epilepsy.

Lancet Neurol 2019
Published Online
November 13, 2019

Comment

Cenobamate: new hope for treatment-resistant epilepsy

A third of patients with epilepsy worldwide are in need of more effective anticonvulsive drugs, since their epileptic seizures remain uncontrolled with currently available medical treatments.[1] To date, despite that a dozen new drugs have been developed in the past 20 years, the chance of complete seizure control after failure of two anticonvulsant treatments, even in patients with newly diagnosed epilepsy, is low.[2] In *The Lancet Neurology*, Gregory Krauss and colleagues[3] report results of the second phase 2 double-blind, randomised, placebo-controlled, dose-response trial on the safety and efficacy of adjunctive cenobamate (YKP3089) for the treatment of focal epilepsy. The mechanism of action of this drug is still under investigation. Beside inhibiting excitatory sodium-channel currents, it is believed that cenobamate enhances inhibition by modulation of GABAA receptors.

Lancet Neurol 2019
Published Online
November 13, 2019

> "…*seizure freedom is of great clinical significance to patient quality of life and the rates reported in this study are notable relative to all other pivotal studies of antiepileptic drug treatment in uncontrolled focal seizures over the past 25 years.*"

> "*A remarkable finding … is the high percentage of patients with 100% seizure control during the 12-week maintenance phase of this study… For individual patients, it is not a seizure reduction of 50% or even higher that counts, since this effect will not allow them to drive a car or to work under circumstances bearing increased health risks… It is complete seizure control that gives rise for hope of an independent lifestyle.*"

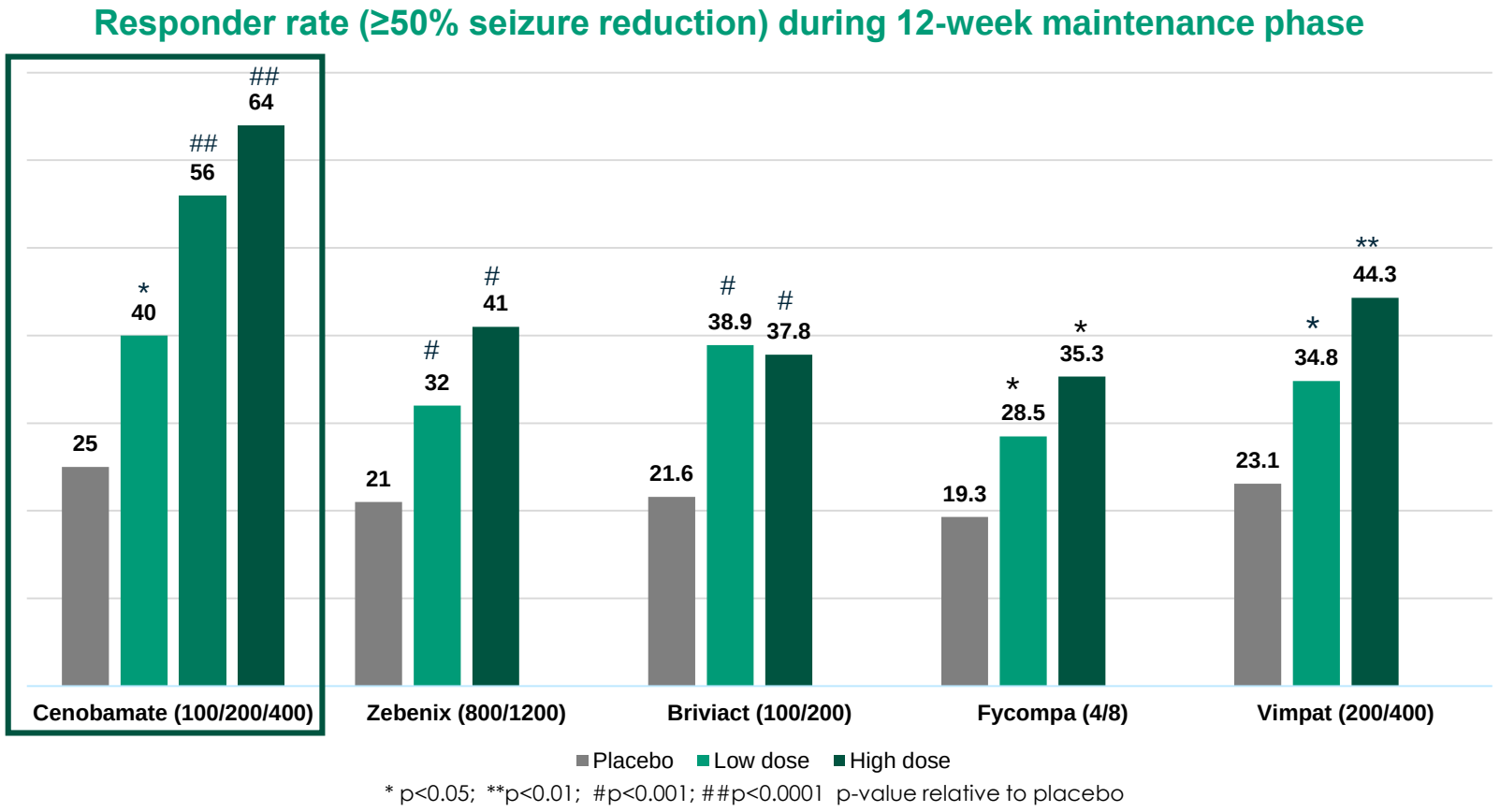
> "*To my knowledge, a seizure freedom rate of 20% or higher has not yet been reported in a placebo-controlled, double-blind trial of anticonvulsive drugs.*"

> "*The high efficacy of cenobamate found in the two phase 2 clinical trials led to the decision of the US Food and Drug Administration (FDA) that no additional efficacy studies were needed.*"

Krauss GL, *et al.*, Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. *Lancet Neurol.* 2019; (published online Nov 13)

Arnold S, Cenobamate: a new hope for treatment-resistant epilepsy. *Lancet Neurol.* 2019; (published online Nov 13)

STUDY C017: UNPRECEDENTED RESPONDER RATE; INDIRECT COMPARISON TO OTHER AEDs



Note: Not based on actual head-to-head clinical data

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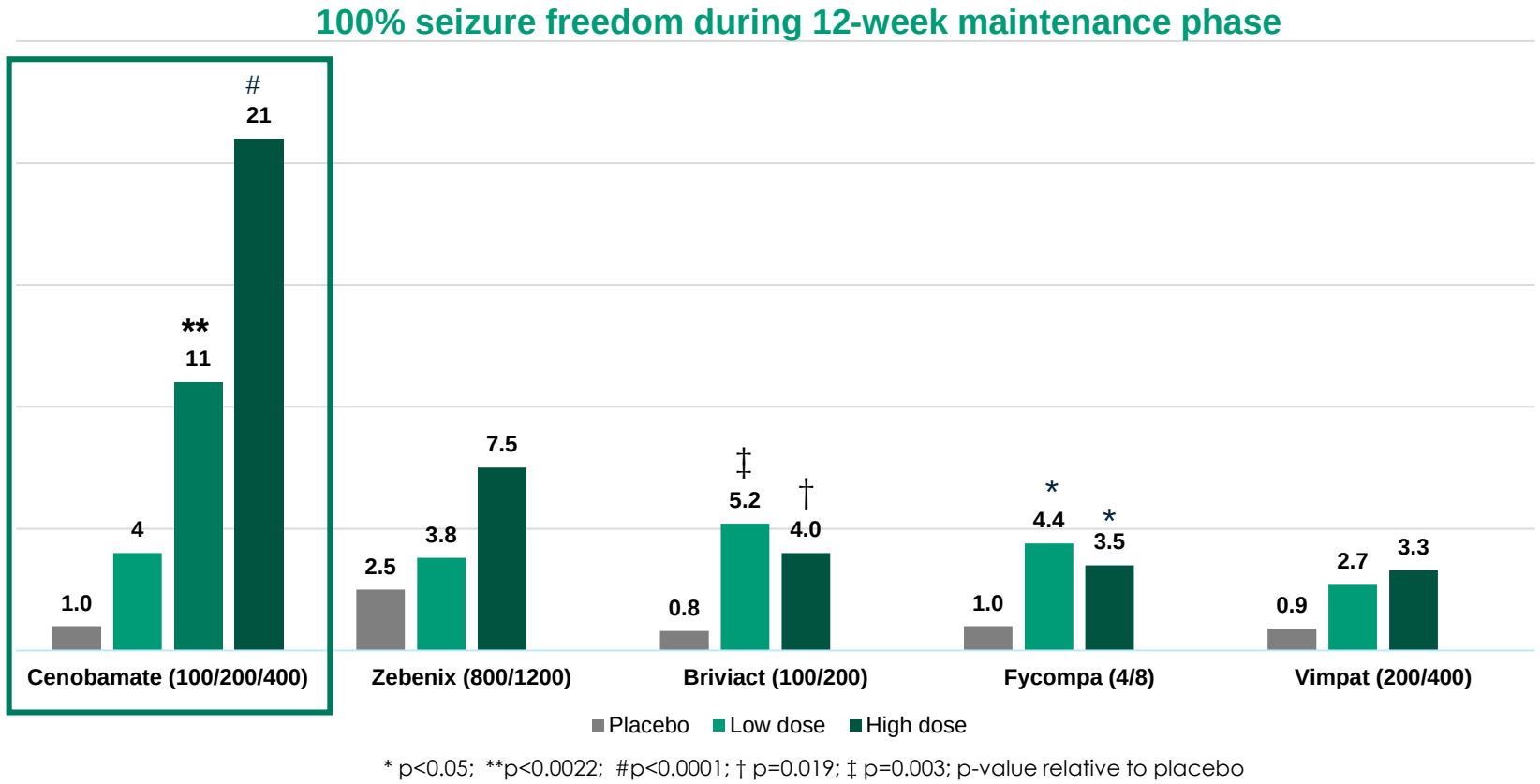
Cenobamate: Krauss et al, *Lancet Neurology*. 2019 Nov (published online Nov 13, 2019); Zebenix: Gil-Nagel et al, *Epilepsia*. 2013 Jan;54(1):98-107; Briviact: Klein et al, *Epilepsia*. 2015 Dec;56(12):1890-1898; Fycompa: Steinhoff et al, *Epilepsia*. 2013 Aug;54(8):1481-9; Vimpat: Sake et al, *CNS Drugs* 2010; 24 (12): 1055-1068.

STUDY C017: CENOBAMATE DELIVERS SIGNIFICANT SEIZURE FREEDOM; INDIRECT COMPARISON TO OTHER AEDs



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STUDY C017: ADVERSE EVENTS (AEs) OCCURRING IN ≥5% OF SUBJECTS AND DISCONTINUATION RATES

% of patients	PBO (N = Placebo108)	CENO 100 mg (N = 108)	CENO 200 mg (N = 110)	CENO 400 mg (N = 111)
Somnolence	8	19	21	37
Dizziness	14	18	20	33
Fatigue	8	12	17	24
Diplopia	2	7	10	15
Headache	6	10	11	11
Nausea	1	7	1	9
Gait Disturbance	3	1	6	8
Constipation	1	2	3	9
Balance Disorder	0	3	2	9
Nystagmus	1	3	4	6
Ataxia	1	2	4	6
Dysarthria	0	2	3	6
TEAEs that Led to Discontinuation in ≥ 2% of Subjects in Any Treatment Group				
Any TEAEs	4.6	10.2	13.6	19.8
Ataxia	0	0	2.7	3.6
Dizziness	0	0.9	0.9	3.6
Somnolence	0	0.9	1.8	2.7
Nystagmus	0	0	0.9	2.7
Vertigo	0.9	0	0.9	2.7

Adverse Events (AEs) and Treatment Emergent AEs (TEAEs) that led to discontinuations during double-blind period (6-week titration + 12-week maintenance period)

- In general, cenobamate was well tolerated
- AEs increased at the highest dose; however, rates of discontinuation for these AEs were low

STUDY C021: PHASE 3 OPEN-LABEL 12-MONTH SAFETY STUDY

- Study C021 was designed following discussions with FDA to characterize the rate of hypersensitivity reactions (DRESS)[1]
  - Lower initial dose and slower titration rate utilized as three cases of DRESS were observed with the higher starting doses and faster titration in the early program
- Titration Phase 12 weeks + Maintenance Phase 40 weeks + extension; n=1347 subjects enrolled
- No cases of DRESS were observed; >1000 subjects exposed to cenobamate for over 1 year
- Most common adverse events were somnolence, dizziness, and fatigue

Study C021 titration schedule:

Week 1 & 2	Week 3 & 4	Week 5 & 6	Week 7 & 8	Week 9 & 10	Week 11 & 12	Week 12+
12.5 mg QD	25 mg QD	50 mg QD	100 mg QD	150 mg QD	200 mg QD	+ 50mg QOW to max 400 mg QD

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1. DRESS: drug reaction with eosinophilia and systemic symptoms. DRESS/hypersensitivity warnings appear in the majority of AED labels.

KOLs INVOLVED IN CENOBAMATE TRIALS ARE ANXIOUSLY AWAITING ITS LAUNCH

Jacqueline A. French, MD
NYU Langone
Professor, Department of Neurology

- She has a patient who has been seizure-free for years and now on monotherapy.
- She can't imagine EMA would require any more data.
- "This drug is terrific."

Michael R. Sperling, MD
Thomas Jefferson University
Director, Jefferson Comprehensive Epilepsy Center

- Knew this was different from the very first trial (013) because his refractory patients were getting better.
- Noted that out of 51 subjects in study 021, about 47 are still on drug.
- Patients no longer progressed to generalized seizure

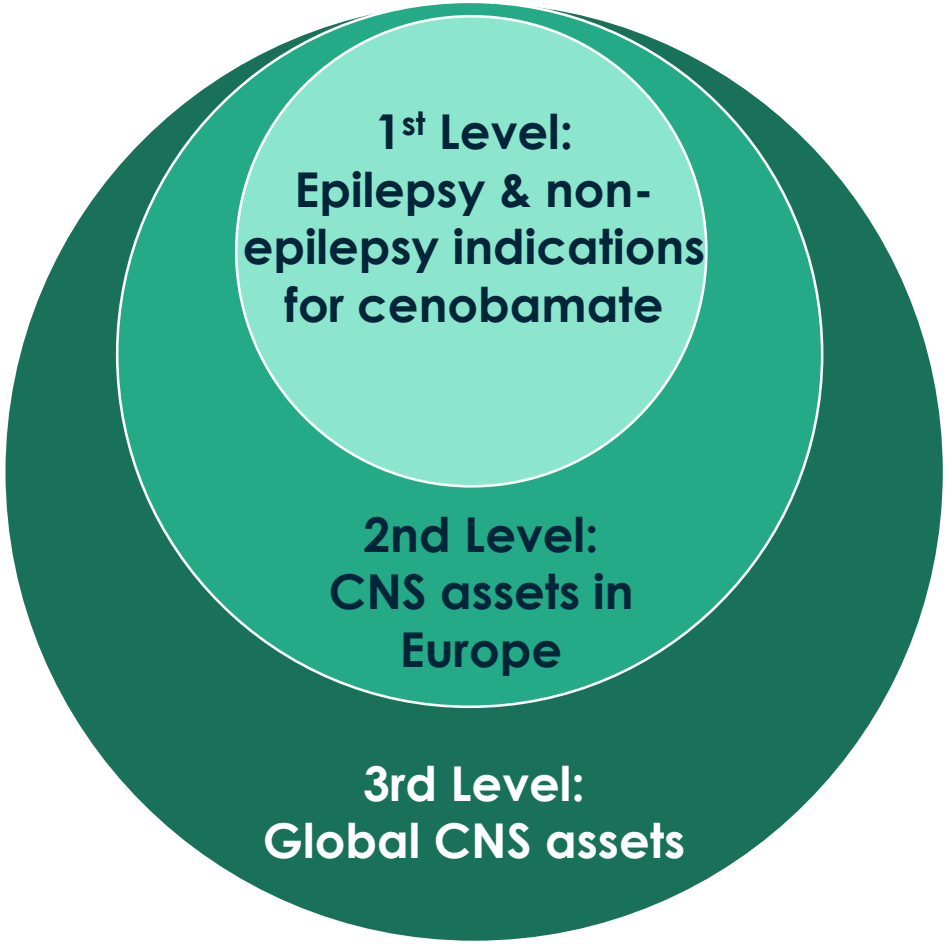
Christian Brandt, MD
Bethel Epilepsy Center
Head of General Epileptology Department, Germany

- Has never seen a drug like this in his decades of clinical trial experience.
- His experience at his site matches the overall data seen.
- Even his most conservative colleagues are excited about the potential for this drug.

"This drug [cenobamate], based on my opinion after treating more than 60 patients, is the most ***startlingly effective anticonvulsant*** drug that I've ever used in an investigational trial. I've been involved [in] investigational trials since the late 1980s and this one ***remarkably reduces seizure frequency and seizure severity***. I have seen a number of patients who have become ***seizure-free after starting this drug***."

(published interview with Michael R. Sperling, MD, January 2019, NeurologyLive.Com)

THE LONG-TERM VISION FOR ARVELLE IS TO BUILD A GLOBAL CNS COMPANY



Arvelle envisions three pillars to its long-term vision:

1. Develop key additional epilepsy and non-epilepsy indications for cenobamate
2. Leverage the Arvelle commercial footprint with additional late-stage CNS assets in Europe
3. Identify assets that can allow Arvelle to expand beyond Europe

BEYOND FOCAL ONSET SEIZURES – CENOBAMATE A "PIPELINE IN A PRODUCT"

Program	Indication	Status	Timeline
		Phase I / Phase II / Phase III / Regulatory	
Epilepsy	Focal-Onset Seizures	Pre-filing	MAA filing expected H1:2020
	Primary Generalized Tonic-Clonic Seizures	Ph III	Expected to complete in 2022
	Pediatric / Orphan	Ph 1/Ph II	Expected to initiate in 2020
Non-Epilepsy	Bipolar Disorder	Ph II	Under evaluation, programs could begin in late 2020
	Neuropathic Pain	Ph II	
	Anxiety Disorders	Ph II	

- Non-epilepsy indications under consideration with SK Life Science
- Potential indications supported by strong mechanistic rationale and non-clinical data

SUMMARY: ARVELLE THERAPEUTICS

- Initial focus on development and commercialization of cenobamate in Europe
- Cenobamate is clearly differentiated from current standard of care on the market's most important unmet need: **seizure freedom**
- The treatment resistant epilepsy market is large, with **~1M patients** across Europe
- Arvelle only needs a **small commercial footprint** due to epilepsy referral patterns
- There are **multiple potential catalysts** in the near term:
  - Potential US FDA approval (PDUFA Nov 21, 2019; SK Life Science)
  - MAA filing H1 2020 (by Arvelle; remaining negotiation is PIP[1])
  - MAA approval and immediate EU launch expected H1 2021
- Arvelle's long-term vision is to build a global CNS company
- The company is well capitalized and has raised $207.5M to date

1. PIP: Paediatric Investigation Plan

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www.arvelletx.com

info@arvelletx.com