Rhythm Pharmaceuticals

Third Quarter 2021 Financial Results

November 2, 2021

On Today's Call

David Meeker, MD, Chair, President and Chief Executive

Linda Shapiro Manning, MD, PhD, Chief Medical Officer

Jennifer Chien, EVP, Head of North America

Hunter Smith, Chief Financial Officer

Forward Looking Statements

This presentation contains certain statements that are forward-looking within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and that involve risks and uncertainties, including without limitations statements regarding the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, including the anticipated timing for initiation of clinical trials and release of clinical trial data and our expectations surrounding potential regulatory submissions, approvals and the timing thereof, our business strategy and plans, including regarding commercialization of setmelanotide, the application of genetic testing and related growth potential, expectations surrounding the potential market opportunity for our product candidates, the sufficiency of our cash, cash equivalents and short-term investments to fund our operations, and strategy, prospects and plans, including regarding the commercialization of setmelanotide. Statements using words such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including but not limited to, our ability to enroll patients in clinical trials, the outcome of clinical trials, the impact of competition, the impact of management departures and transitions, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our expenses, the impact of the COVID-19 pandemic on our business operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q and other reports we file with the Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this presentation or to update them to reflect events or circumstances occurring after the date of this presentation, whether as a result of new information, future developments or otherwise.

David Meeker, MD

Build Strategy Focused on Maximizing Patient Access to Setmelanotide

U.S. IMCIVREE commercial availability meeting expectations

Strong foundation for Bardet-Biedl commercial opportunity in mid-2022

Market access, reimbursement advancing in key international markets

Clinical development expansion meaningfully increases addressable patient population

Multiple Highlights and Continued Execution in Third Quarter of 2021

U.S. IMCIVREE commercial availability meeting expectations

- 3Q21 net sales > $1M
- Continued progress in securing access, reimbursement in key international markets

Advancing towards BBS U.S. launch in mid-2022

- Strong regulatory submissions filed in both U.S. and EU
- BBS field force fully deployed, engaging physicians

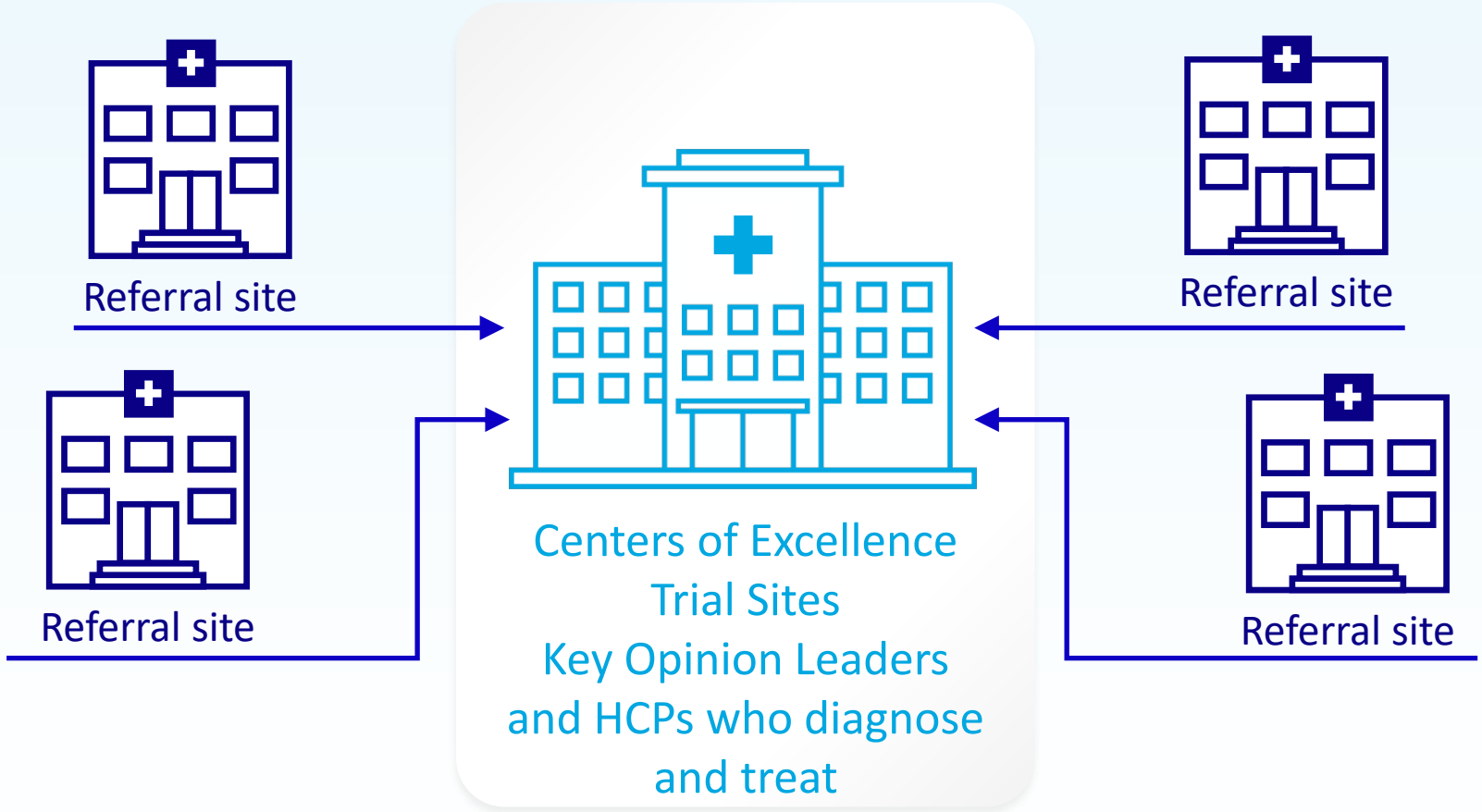
22 presentations at major medical conferences

- Positive data updates across all programs and indications
- World-renown KOLs presenting setmelanotide HRQOL, hunger and weight loss data

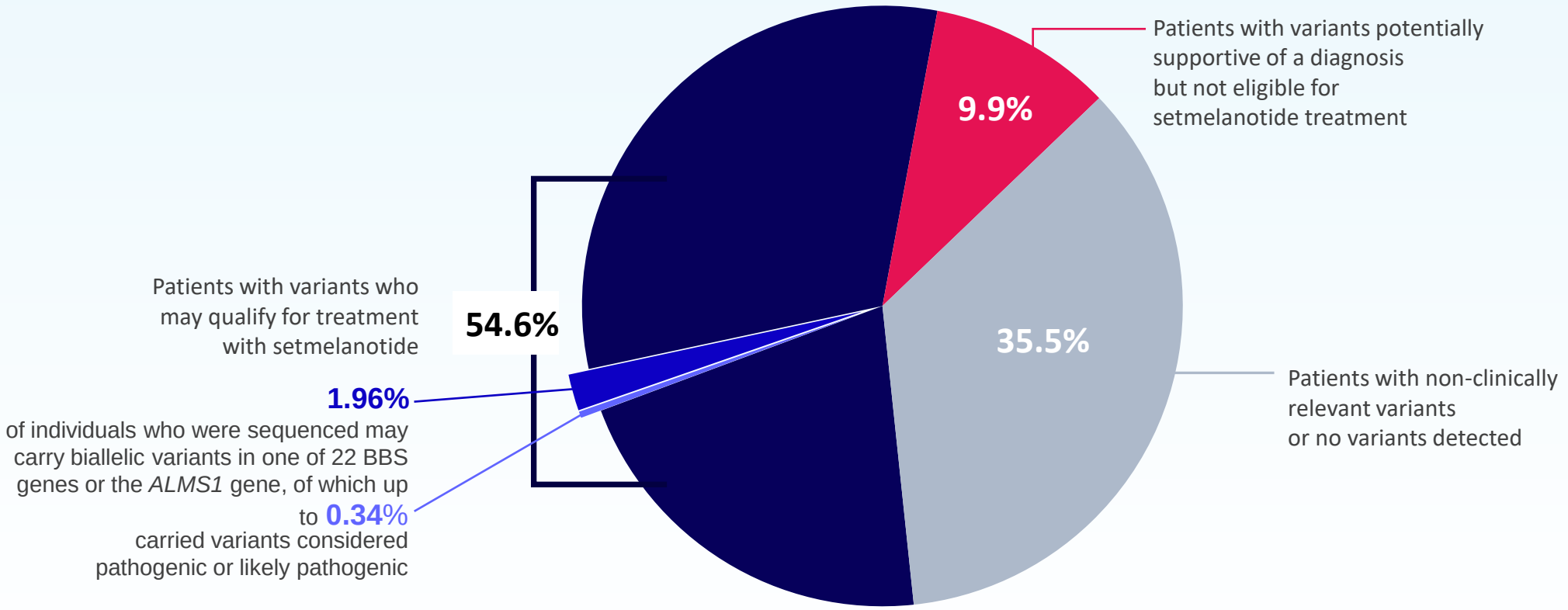
Clinical development programs on track

- URO updates suggests >50% hit rate for trial-eligible variants
- EMANATE, DAYBREAK, pediatrics and weekly trials advancing to FPI

Community Building Strategy Focuses on Building Referral Networks for Rare Genetic Diseases of Obesity

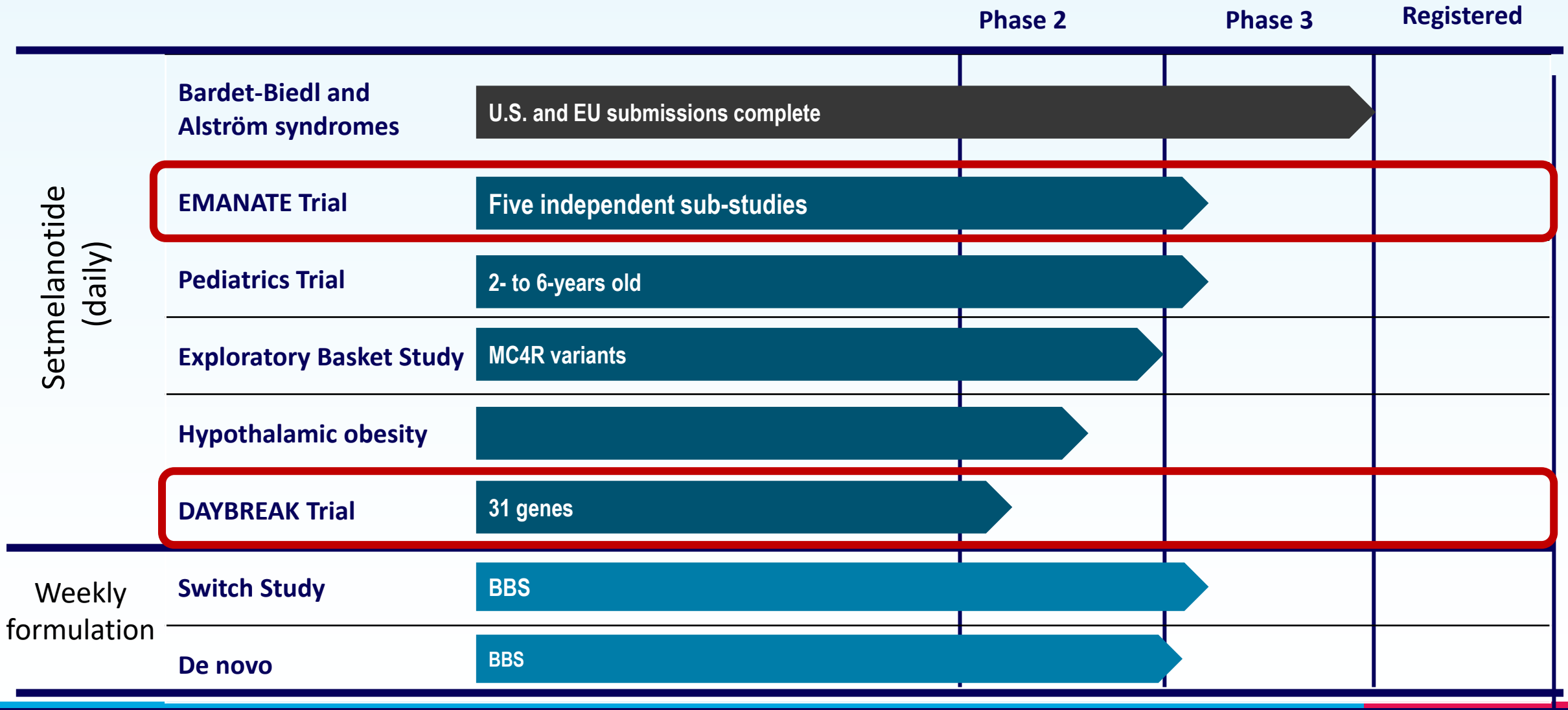


Uncovering Rare Obesity® Shows that 54% of Sequenced Individuals with Severe Obesity Carry Variants in Genes with Known Relevance to MC4R Pathway



* Represents a weighted yield from 8,599 URO samples collected as of July 12, 2021. Prior to May 2021, Rhythm's URO panel tested for variants in 40 obesity-related genes, including 11 genes eligible for the DAYBREAK or EMANATE trials; data for those 11 genes is available in all 8,599 samples. Rhythm launched URO 2.1/3.0 in early May 2021, which now sequences 79 obesity-related genes and the 16p11.2 chromosomal region, including 25 additional DAYBREAK/EMANATE genes. Data on all 79 genes (including all 36 DAYBREAK/EMANATE genes) was available for 788 patients, and then used to calculate a weighted yield across the total study population.

Clinical Programs Designed to Achieve Label Expansion on Track



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Linda Shapiro, MD, PhD

Regulatory and Clinical Update

Update on Bardet-Biedl syndrome

Setmelanotide is Poised to be First-ever Therapy to Address Unmet Needs of Hyperphagia and Obesity in Patients with BBS

1

Severe obesity, hyperphagia from an early age affect the health and quality of life for patients and their families and caregivers

2

U.S. and EU regulatory submissions completed

3

Additional compelling data about the impact of setmelanotide

- PBO controlled weight loss data (ESPE)
- Meaningful QOL improvements (TOS)

Hyperphagia's Severe Impact on Lives of Patients with BBS and their Caregivers

> *…I constantly felt like I was failing…. because if I did not give her extra food, then I felt terrible for denying her that when I knew she felt like she was starving, and if I did give it to her, I felt like I was slowly killing her and causing her health problems."*

Caregiver

> *We had put locks on the fridge at one point to kind of keep her from eating cheeses."*

Caregiver

> *I was eating pretty much whatever, whenever and wasn't able to stop myself from eating or sneaking food in the middle of the night."*

Patient

> *She couldn't do as well in school because she was thinking about what was in her lunchbox or what she was going to get at lunch …"*

Caregiver

> *…At one point [~2 years old], he found where the white flour was…. and was able to pull the container out of the pantry and just sat down and was eating flour."*

Caregiver

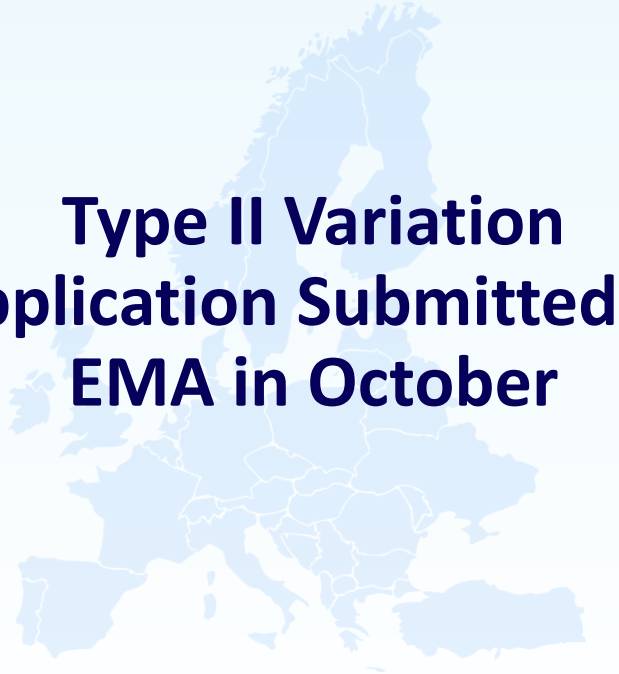
Excerpted from in-depth qualitative interviews with patients with BBS and/or their caregivers who were participating in an open-label extension study of setmelanotide.

U.S. and EU Regulatory Submissions for BBS and Alström Syndrome Recently Completed

Pivotal Phase 3 trial met all primary and key secondary endpoints*

sNDA Submitted to U.S. FDA in September

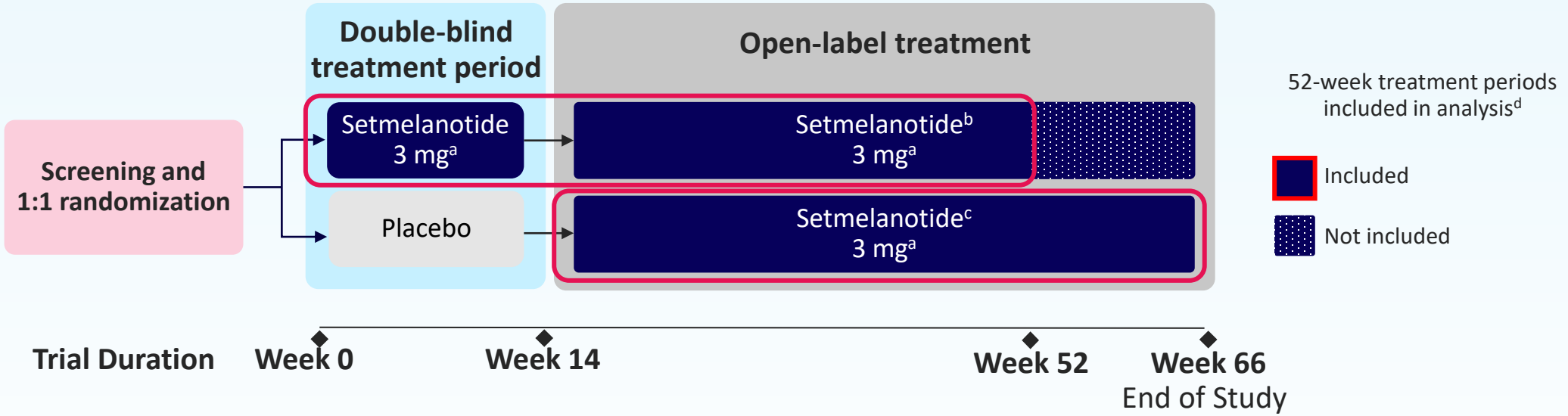
U.S projected commercial launch mid-2022



Type II Variation Application Submitted to EMA in October

*All patients who met the primary endpoint defined as more than 10 percent weight loss had BBS and none had Alström syndrome.

Phase 3 Trial to Evaluate Setmelanotide Therapy for 52 Weeks with 14-week Placebo-controlled Period in Patients With BBS



Key inclusion criteria[1]

- Clinical diagnosis of BBS or Alström syndrome
- ≥6 years of age
- Obesity
  - ≥16 years: BMI ≥30 kg/m^2
  - 6–15 years: weight >97th percentile for age and sex

Key exclusion criteria

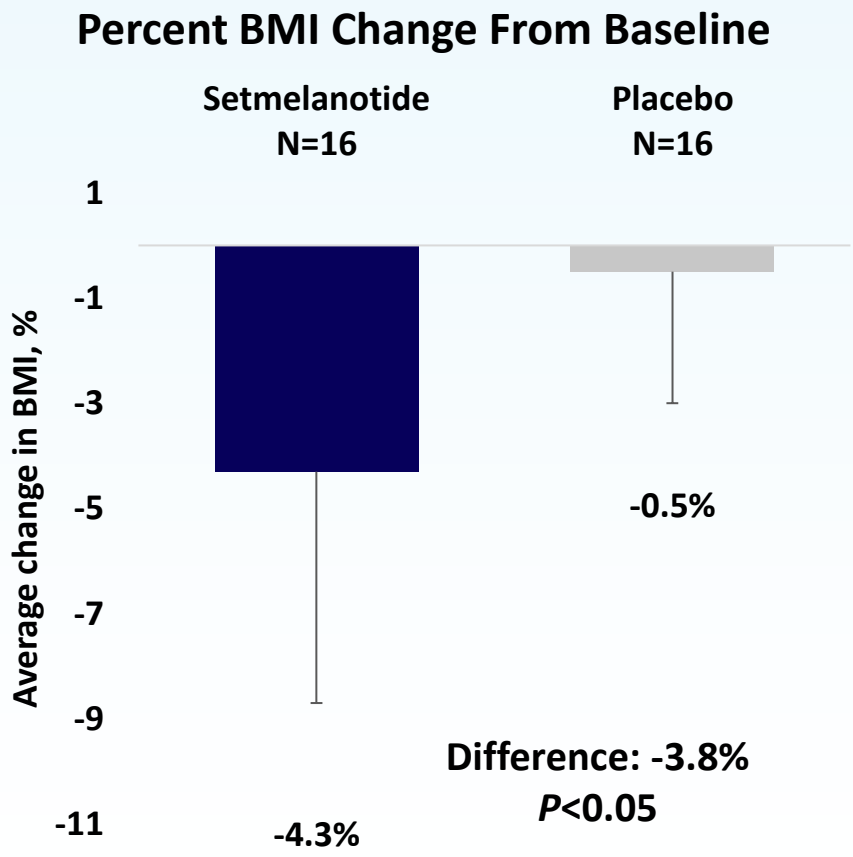
- Recent (within 2 months) intensive diet and/or exercise resulting in >2% weight loss
- Use of approved obesity medication within 3 months of randomization
- Prior gastric bypass resulting in >10% weight loss durably maintained
- Glomerular filtration rate <30 mL/min

[a]Dose escalation based on age up to 3.0 mg. [b]For patients who received >52 weeks of setmelanotide at the end of study, analysis was performed for 52 weeks of setmelanotide. [c]A multiple imputation model was used to impute data in patients who received <52 weeks of setmelanotide at the time of the analysis. [d]Efficacy outcomes were assessed at 52 weeks on active treatment for each study group (ie, Week 0 to 52 for the setmelanotide group and Week 14 to 66 for the group assigned to placebo during the double-blind treatment period). **1.** Haws et al. *Contemp Clin Trials Commun*. 2021;22:100780.

Setmelanotide Led to Significant BMI Reduction in Patients with BBS Versus Placebo at Week 14

14-week PBO data

Patients with BBS treated with setmelanotide achieved an average BMI reduction of **–1.5 kg/m²** **(–3.8%)** at Week 14 compared with patients on placebo who saw ***negligible weight loss*** (*P*<0.05)



As presented at ESPE 2021 – 59th Annual European Society for Paediatric Endocrinology Meeting, September 2021.

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Setmelanotide Achieved Clinically Significant Reduction in BMI in Patients with BBS in Phase 3 Trial at Week 52

–9.1% mean % change in BMI in patients ≥18 years old

–9.5% mean % change in BMI in patients <18 years old

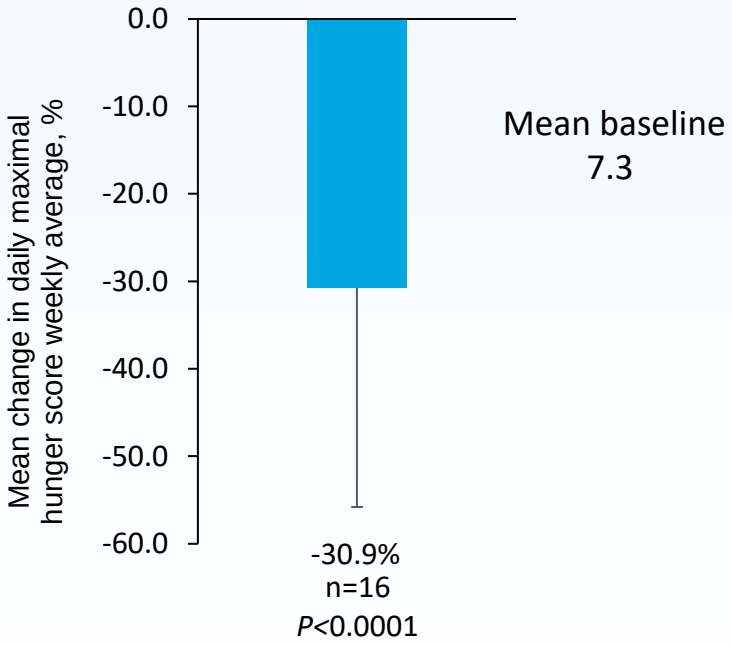
	Baseline	52 weeks on active treatment	Percent change from start of active treatment
Mean (SD) BMI in those ≥18 years old (n=15[a])	**46.4 kg/m²** (5.8)	**43.3 kg/m²** (7.2)	**–9.1** (6.8)
Mean (SD) BMI in those <18 years old (n=16[b])	**37.4 kg/m²** (9.4)	**34.2 kg/m²** (10.1)	**–9.5** (6.4)

[a]n=15 at baseline and 12 after 52 weeks on active treatment. [b]n=16 at baseline and 14 after 52 weeks on active treatment.
As presented by Dr. Robert Haws at ObesityWeek 2021

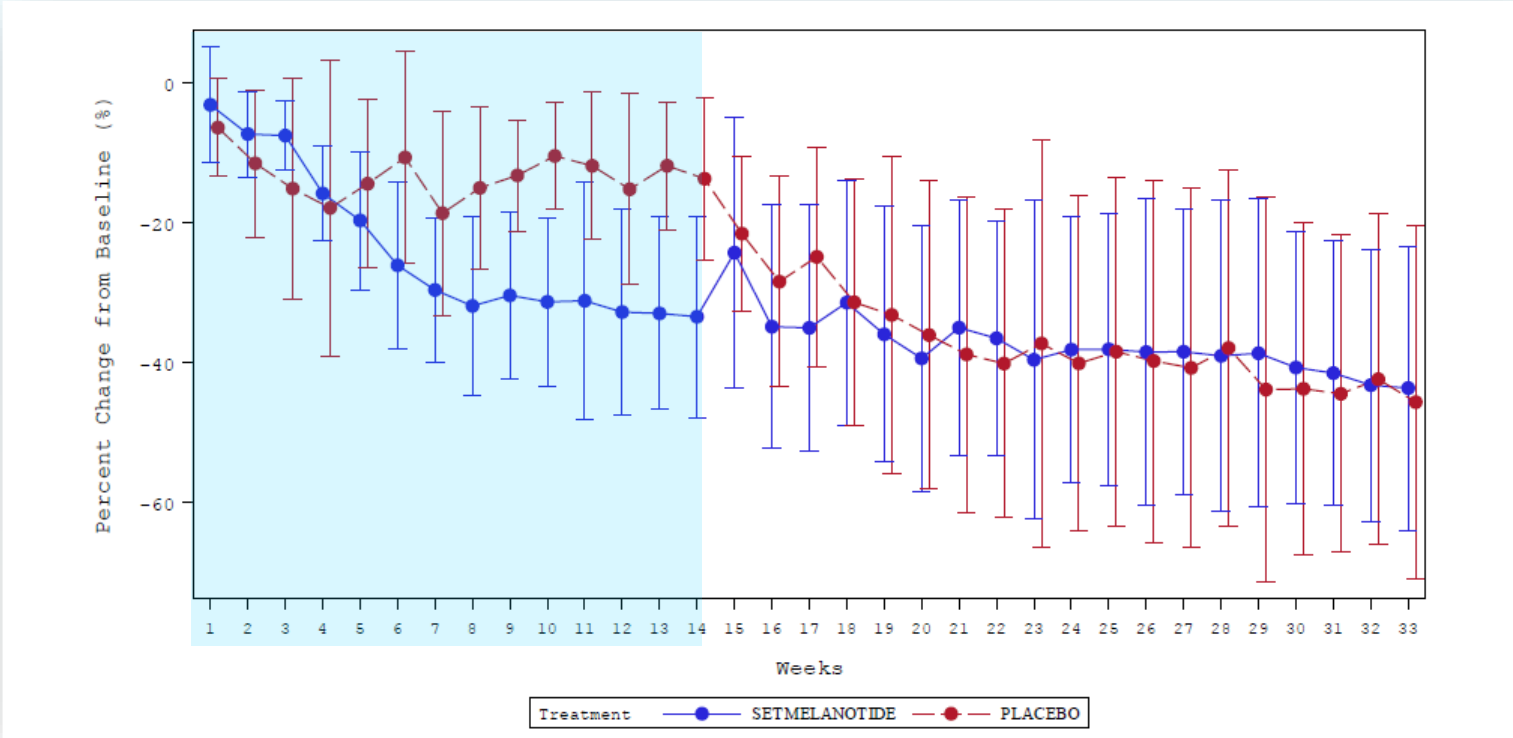
Setmelanotide Achieved Clinically Meaningful Reduction in Hunger in Adults and Children with BBS at Week 52

62.5%

(95% CI, 35.4%–84.8%; *P*<0.0001)
of participants achieved
≥25% reduction in daily maximal hunger score



Data show separation in hunger reduction during placebo period followed by placebo group reaching treatment levels rapidly after crossover



Daily most hunger score weekly average percent change from placebo-controlled period baseline by week among participants without cognitive impairment who were 12 years old or older. Data on file at Rhythm.

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Setmelanotide Achieved Clinically Meaningful Improvements in Health-related Quality of Life (HRQOL)

85% of patients reported clinically meaningful improvements or preserved non-impaired health related quality of life status

Impact of Setmelanotide on HRQOL		
	Adults (≥18 years old)	Children (8-17 years old)
Patients, n	11	9
	IWQOL-Lite total score*	PedsQL total score**
Baseline, mean (standard deviation)	74.9 (12.6)	67.2 (18.9)
Change at week 52, mean (SD)	**+12.0 (10.8)**	**+11.2 (14.4)**

***Impact of weight on quality of life or IWQOL:** Is a zero to 100 range, with zero being the worst possible and 100 best possible score. A total score increase of 7.7 to 12 is considered clinically meaningful improvement; Pre-defined ranges are: Impairment: <71.8 = severe, 71.9-79.4 = moderate, 79.5-87.0 = mild, 87.1-94.6 = none.
****Pediatric quality of life inventory or PedsQL:** Also zero to 100, with zero being the worst and 100 best possible score. A total score increase of 4.44 or greater is considered clinically meaningful. Impairment is defined as a score < 68.2.

Clinical development programs on track to expand patient population

Setmelanotide Clinical Development Programs on Track to Expand Patient Populations with Impaired MC4R Pathway

1

Patients with heterozygous variants in POMC, PCSK1 and LEPR associated with a severe phenotype similar to patients with homozygous variants

2

Growing body of evidence that supports setmelanotide's potential to deliver clinically meaningful weight loss and improvements in hyperphagia

3

EMANATE and DAYBREAK trials start-up activities underway;

Weekly and pediatrics trials, too

Similar Severe Phenotype Associated with both Heterozygous and Homozygous Variants in LEPR, POMC, and PCSK1

In new research, patients with heterozygous variants characterized by severe and early-onset obesity with food impulsivity

- Severe phenotype: Comparable BMI between homozygous and heterozygous carriers
- Hyperphagia present in 90% of het adults (86% of het children)
- Frequent endocrine and neurodevelopmental abnormalities present in het variant carriers

Largest longitudinal cohort comparison between homozygous (n=16) and heterozygous (n=60) POMC, PCSK1 and LEPR patients

Journal of Clinical Endocrinology & Metabolism

https://doi.org/10.1210/clinem/dgab404

Courbage S, et al. J Clin Endocrinol Metab. 2021;106:2991-3006.

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Rhythm Delivers Multiple Presentations at Major Medical Conferences

ESPE 2021: New setmelanotide Phase 2 Basket study data show at three months:

- **30%** (9 of 30) of patients with obesity due to variants of the SRC1 gene achieved clinically meaningful weight loss or BMI-Z reduction
- **43%** (15 of 35) of study participants with obesity due to variants of the SH2B1 gene achieved clinically meaningful weight loss or BMI-Z reduction
- Clear separation between patients who responded to setmelanotide treatment at three months and those who did not

EMANATE and DAYBREAK Trials Start-up Activities Underway

Trial sites

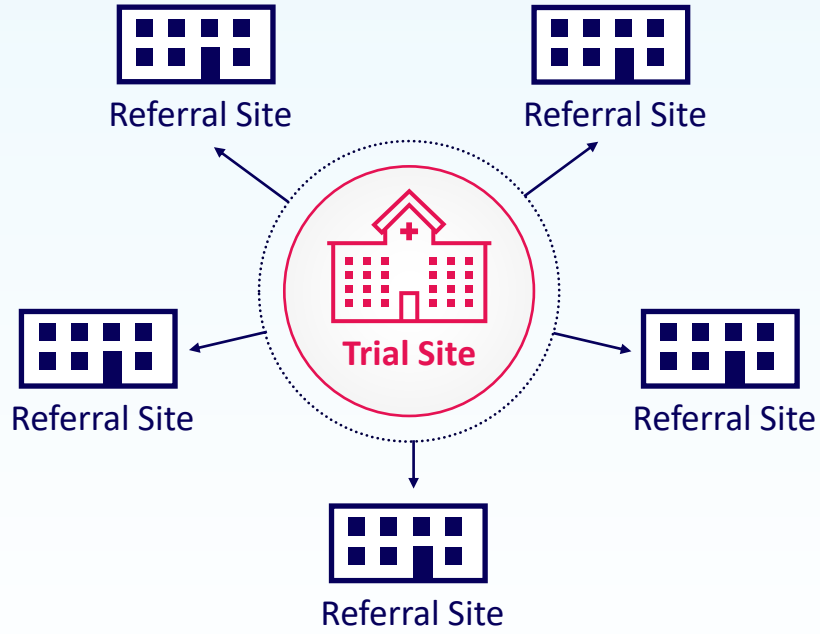
- 75+ sites identified in 14 countries in North America, Europe and the Middle East
- Site initiations ongoing; investigator meetings planned in November and December
- First patients in expected in Q4 2021 or Q1 2022

EMANATE 52-week treatment period

- Five individual sub-studies
- Each may readout, potentially be registered independently

DAYBREAK 40-week treatment period

- 31 genes with ‘strong’ or ‘very strong’ relevance to MC4R pathway
- Individual genes may readout independently



Jennifer Chien
U.S. Commercial Update

IMCIVREE Commercial Sales in U.S. Meeting Expectations

First two quarters of IMCIVREE commercial availability:

- Positive coverage decisions, reimbursement and access
- Continued focus on HCP engagement
- Patient Services and Corporate Accounts teams in place and making a difference

INITIAL PATIENT EXPERIENCE:

38 year old:
Went from being constantly distracted by hunger to forgetting to eat

11 year old:
Mom said: “See, this is not your fault.”

Bardet-Biedl Community is Established and Identified

U.S. prevalence estimated to be

1,500 to **2,500**

patients

More than **600** individuals living with BBS are enrolled in **CRIBBS registry**

Estimated European prevalence estimated to be

~2,500

patients

More than **1,500** individuals identified in **EU4 + UK** at ~20 academic medical centers with >40 BBS patients

Experience with POMC, PCSK1 and LEPR Commercial Availability is Foundational to BBS Launch Strategy

Establish access

Establish market access and patient support for IMCIVREE

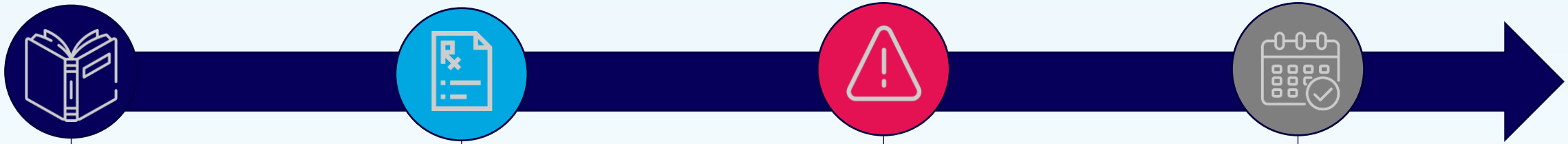
Treat obesity and hyperphagia

Ensure diagnosed BBS patients will be treated for hyperphagia and obesity

Accelerate diagnosis

Facilitate BBS diagnosis and initiate further patient identification

Patient Support Team in Place to Empower Patients through Personalized Engagement



Education

For all patients and families, regardless of treatment status:

- Disease awareness
- Navigating treatment access
- Connection to community resources
- Nutrition and Wellness
- Customized 1x1 and Group programs

Treatment Initiation

For patients and providers:

- Comprehensive onboarding, treatment expectations and injection training
- Partnering with patients and prescribers to identify and resolve treatment related barriers

Access

Support for patients with access barriers:

- Facilitation of drug coverage through benefit Investigation, prior authorization and appeal support
- Copay program for eligible patients
- Free drug program for uninsured, eligible patients

Adherence

Robust, individualized adherence program:

- Real-time missed shipment monitoring and follow-up
- Proactive multi-channel communications program
- Educational materials to address common barriers
- Patient Education Programs

BBS Territory Managers Now in the Field and Focused on Targeted Physician Engagement

TERRITORY MANAGER PROFILE:

20	**6**	**100%**	**6**
Average years pharma/biotech sales experience	Average years rare disease experience	have launch experience	average number of launches per territory manager

New Market Research Highlights Positive Impressions of IMCIVREE Profile

HCPs:

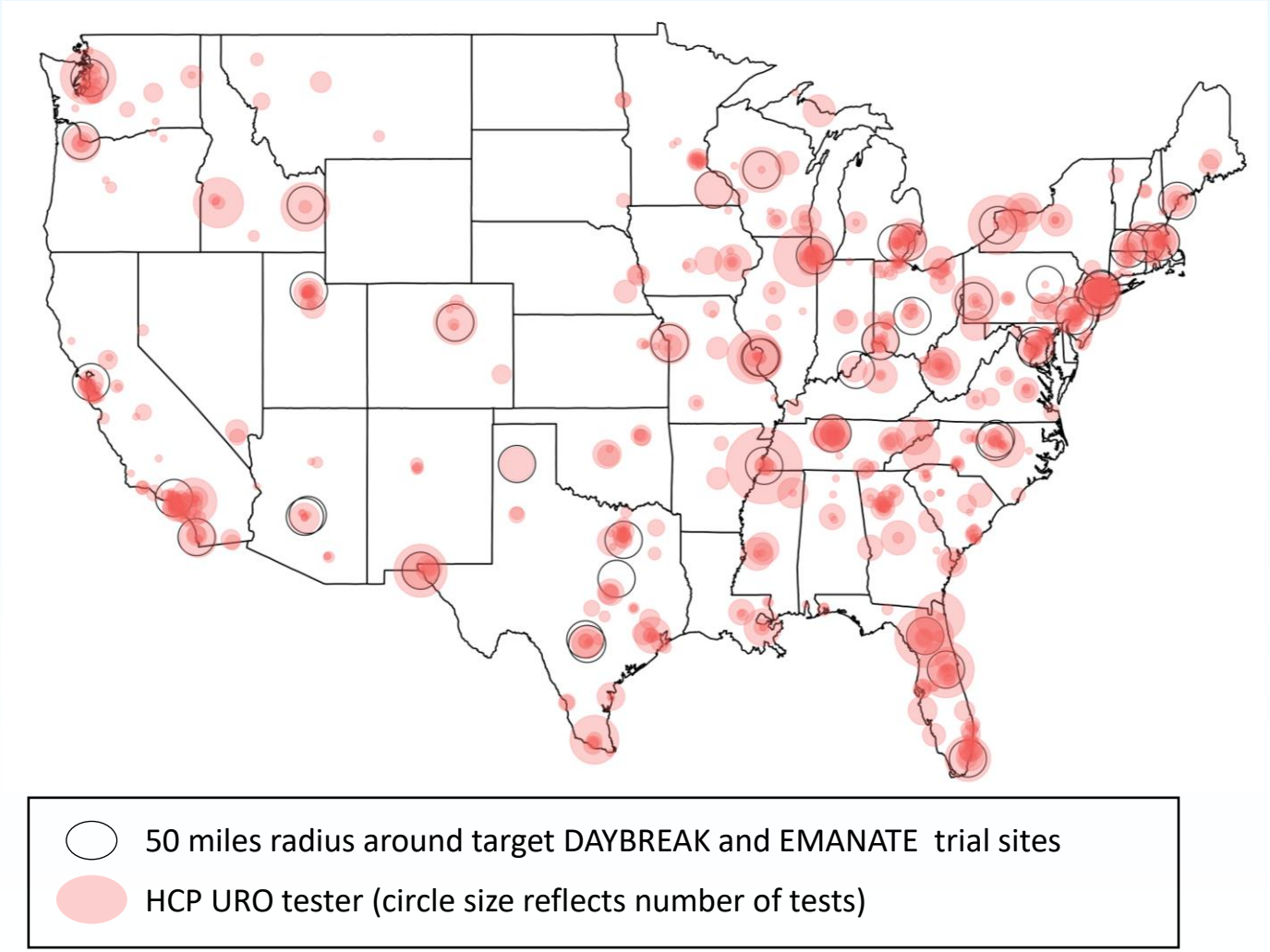
- Obesity was universally viewed as a serious concern in individuals w/ BBS, and cited significant challenges with current options for management
- Strongest attributes and reasons to prescribe: wide age range (6+), mechanism of action, and general effectiveness in weight loss
- Dosing and safety/tolerability all viewed as acceptable, and didn't foresee barriers in initiating treatment

75%

of respondents would prescribe setmelanotide as first-line therapy for obesity in BBS

Double-blind, qualitative primary market research via in-depth, 1-hr telephone interviews with 30 US HCPs who manage obesity in BBS.

Area Development Managers and Targeted URO Strategy Drives Trial Enrollment and Commercial Patient ID



Trial enrollment

- Identifying patients for EMANATE and DAYBREAK trials

Commercial patients

- Genetic identification and confirmation for biallelic POMC, PCSK1 and LEPR

Patients with BBS gene variants

- HCPs with positive BBS test handed off to TMs

Hunter Smith
3Q 2021 Financial Results

Q3 2021 Financial Highlights

($ in millions except as noted, per share data and shares outstanding)	Three months ended September 30, 2021
Product revenue, net	$1.0M
R&D expenses	$27.5M
SG & A expenses	$17.5M
Net loss	$(35.1)M
Shares outstanding (basic and diluted share count)	50,246,303
Net loss per share basic and diluted	$(0.70)
Cash, cash equivalents and short-term investments position (period end)	$328.4M

Cash Expected to be Sufficient to Fund Operations into 2H 2023

David Meeker, MD
Conclusion

Transformational Progress Expected in 2021 and 2022

	1H 2021
✓	Proof-of-concept data in HET patients, SRC1 and SH2B1 deficiency obesities
✓	Update on genetic sequencing and epidemiology data
✓	IMCIVREE commercially available in U.S. for POMC, PCSK1 and LEPR deficiency obesities
✓	Initiate Phase 2 trial in hypothalamic obesity
	2H 2021
✓	EU, Great Britain authorization for POMC, PCSK1 and LEPR
✓	Present full data analyses from pivotal Phase 3 trial in BBS at ESPE and TOS 2021
✓	U.S. and EU regulatory submissions for BBS and AS
	Initiate Phase 2 DAYBREAK trial
	Initiate Phase 3 “switch study” of weekly formulation
	Initiate Phase 3 trial in pediatric patients aged 2-6 years old
	Initiate Phase 3 EMANATE trial *(4Q 2021 or 1Q 2022)*
	1H 2022
	Initiate Phase 3 “*de novo* study” of weekly formulation
	Initial data from Phase 2 Basket study in MC4R-rescuable patients
	Initial data from Phase 2 trial in hypothalamic obesity

Clinical Development Programs Designed to Expand the Setmelanotide Opportunity

Now approved

600 – 2,500**

IMCIVREE® (setmelanotide) injection

Obesity due to POMC, PCSK1 or LEPR deficiency

Potential U.S. launch in mid-2022£

2,000 – 3,000**

Bardet-Biedl and Alström syndromes

Clinical development expansion

Phase 3 EMANATE Trial€

Five independent substudies

45,000†	**Heterozygous POMC/PCSK1 deficiency**
25,000†	**Heterozygous LEPR deficiency**
20,000†	**SRC1 deficiency**
23,000†	**SH2B1 deficiency**
100,000†	**PCSK1 N221D deletion**

Phase 2 DAYBREAK Trial Exploring an additional **31 genes**

** Estimated prevalence of U.S. patients based on company estimates

† Estimated U.S. patients based on population* with early-onset, severe obesity who may benefit from setmelanotide based on sequencing results and current estimated responder rates.

* 1.7% of the US population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018ǂ); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017); £ U.S. and EU regulatory submissions for BBS and Alström syndrome filed in September and October 2021, respectively. € Planned EMANATE trial would include patients with variants classified as pathogenic, likely pathogenic or of uncertain significance, and patients with N221D variant;

Questions