



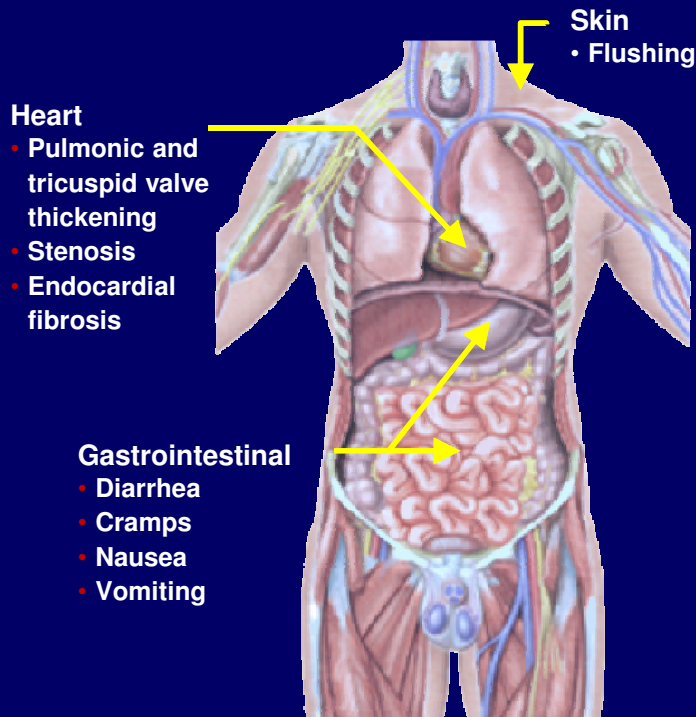
# **Clinical Development in the Treatment of Carcinoid Syndrome**

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**Pablo Lapuerta, MD**

**Executive Vice President and Chief  
Medical Officer**

# Carcinoid Syndrome



- Tumoral release of **serotonin** and other vasoactive substances into the systemic circulation causes carcinoid syndrome<sup>1</sup>
- Treatment with SSAs is associated with improved symptom control, but patients may not maintain adequate control of symptoms<sup>2,3</sup>
- Inhibition of serotonin synthesis with PCPA was previously shown to provide symptom control, but its utility was limited by CNS side effects<sup>4</sup>

CNS=central nervous system; PCPA=para-chlorophenylalanine; SSA=somatostatin analog.

1. Kulke MH, Mayer RJ. *N Engl J Med.* 1999;340:858-868. 2. Rubin J, et al. *J Clin Oncol.* 1999;17:600-606.

3. Strosberg J, et al. *Gastrointest Cancer Res.* 2013;6:81-85. 4. Engelman K, et al. *N Engl J Med.* 1967;277:1103-1108.

# Key Messages

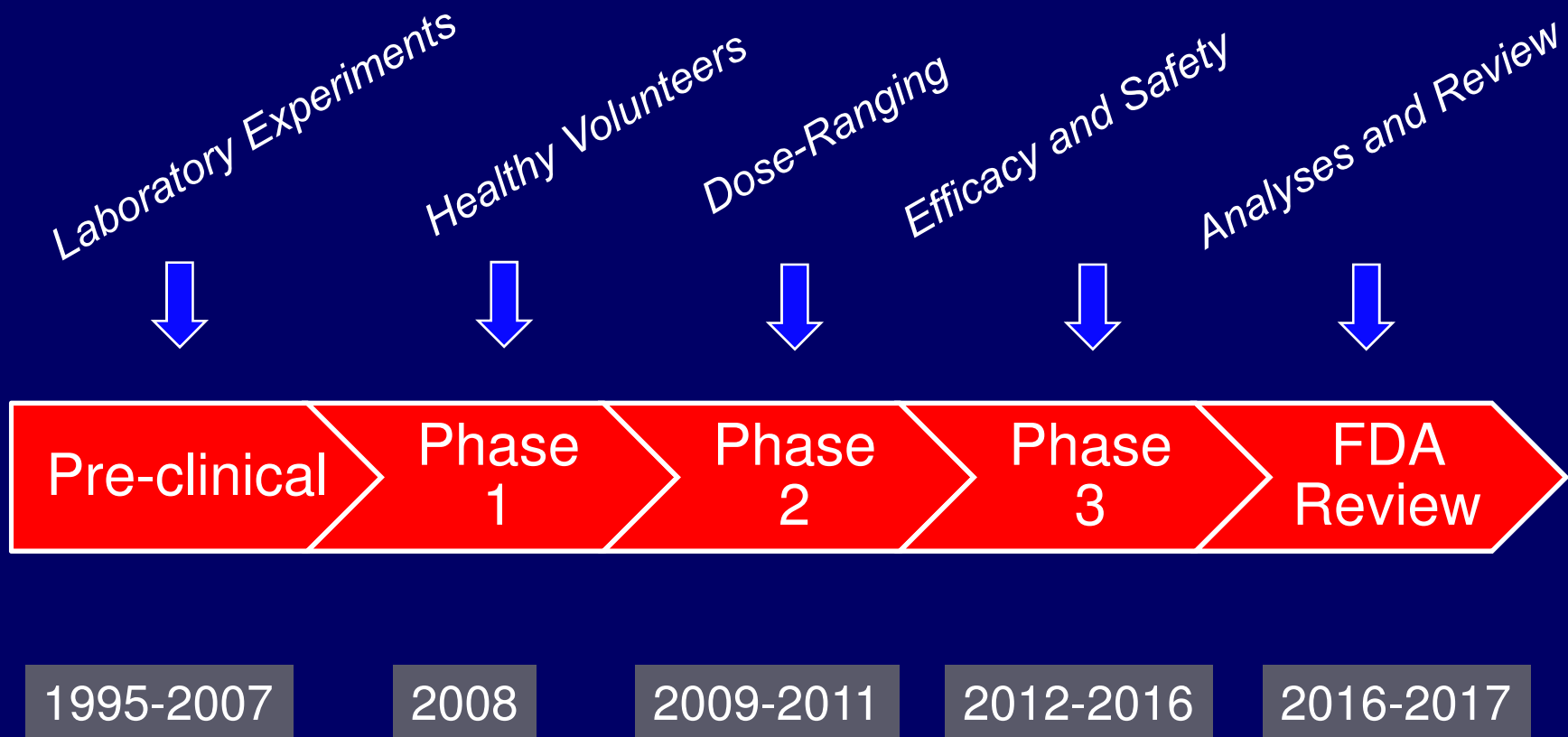
- There are three keys to clinical development
  - Study design
  - Data analysis
  - Patient focus



# Telotristat Ethyl Background

- Telotristat ethyl is an investigational agent
- Top-line results of TELESTAR were recently reported at three scientific meetings
  - the initial, placebo-controlled portion of TELESTAR
  - part of the open-label extension portion of TELESTAR
- Top-line results of TELECAST were recently presented
- Evaluation of the long-term safety and efficacy of telotristat is ongoing
  - TELEPATH

# A Drug Development Timeline



# Pre-Clinical Development

- Developing the mouse model
  - Genetic technology
- Selecting the protein target
  - Discovery biology
- Finding the compound
  - Medicinal chemistry



# Phase 1

- Studies in Healthy Volunteers
  - What is the broad dose range?
  - Are there any early safety issues?
  - Does the drug product inhibit the enzyme in clinic?
    - Is it absorbed effectively?
    - How long does it stay in the bloodstream?
    - Do higher doses provide more inhibition of the enzyme?

*Telotristat Phase 1 Studies Initiated in 2008*

# Phase 1 Progress

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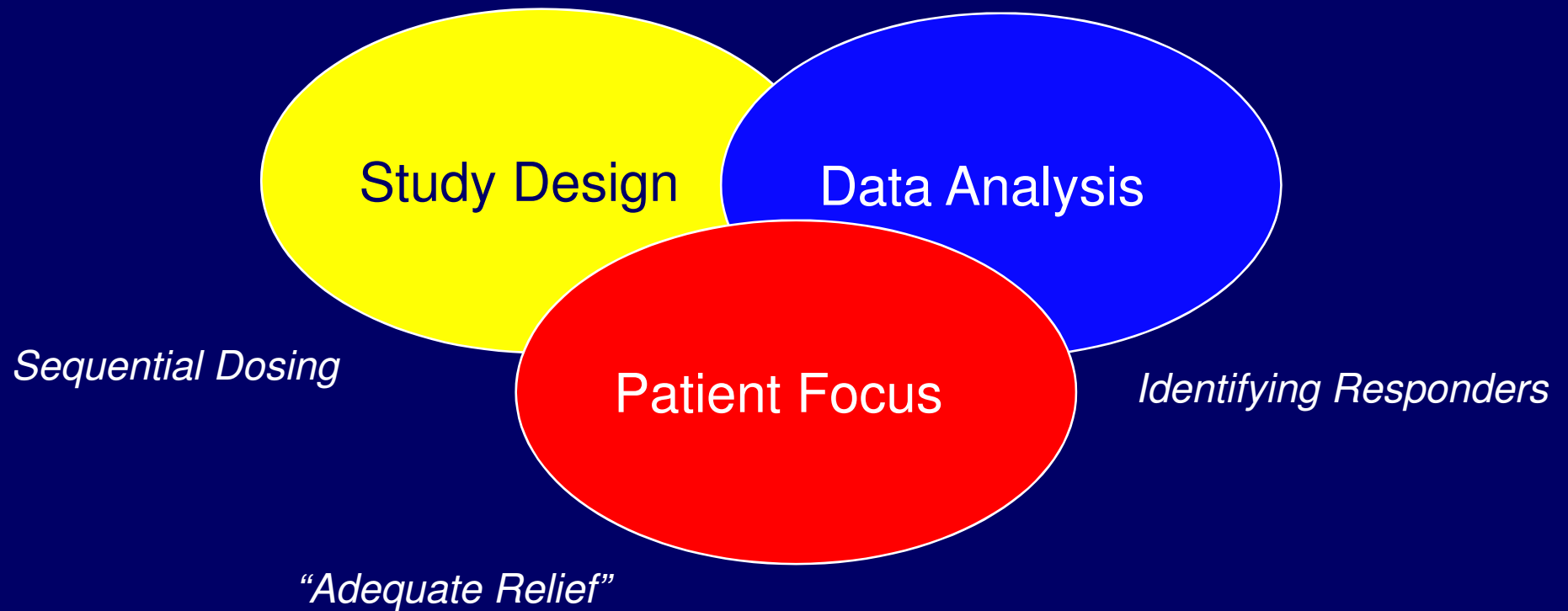
- Dosing 3 times daily is reasonable
- 500 mg was the maximal tolerated dose
- Monitor liver enzymes in Phase 2



# Phase 2: Dose Ranging

- Studying carcinoid syndrome for the first time
- Key questions
  - Is the 500 mg dose tolerated long-term?
  - Could lower doses be effective?
  - What safety monitoring will be needed for Phase 3?
  - What are the best ways to identify efficacy in Phase 3?
    - Bowel movement frequency
    - Stool consistency

# Making the Most of Phase 2



# Phase 2: A Placebo-Controlled Study

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**NIH Public Access**  
**Author Manuscript**  
*Endocr Relat Cancer. Author manuscript; available in PMC 2015 April 01*

Published in final edited form as:  
*Endocr Relat Cancer*. 2014 October ; 21(5): 705–714. doi:10.1530/ERC-14-0173.

**Telotristat Etiprate, a Novel Serotonin Synthesis Inhibitor, in Patients with Carcinoid Syndrome and Diarrhea Not Adequately Controlled by Octreotide**

Matthew H. Kulke<sup>1</sup>, Thomas O'Dorisio<sup>2</sup>, Alexandria Phan<sup>3</sup>, Emily Bergsland<sup>4</sup>, Linda Law<sup>5</sup>, Phillip Banks<sup>5</sup>, Joel Freiman<sup>5</sup>, Kenny Frazier<sup>5</sup>, Jessica Jackson<sup>5</sup>, James C. Yao<sup>3</sup>, Larry Kvoils<sup>6</sup>, Pablo Lapuerta<sup>5</sup>, Brian Zambrowicz<sup>5</sup>, Douglas Fleming<sup>5</sup>, and Arthur Sands<sup>5</sup>

NIH-PA Author Manuscript

*23 Patients*  
*4 Weeks of Placebo-Controlled Treatment*

# Phase 2: An Open-Label Study

ORIGINAL ARTICLE

## Telotristat Etiprate for Carcinoid Syndrome: A Single-Arm, Multicenter Trial

Marianne Pavel, Dieter Hörsch, Martyn Caplin, John Ramage, Thomas Seufferlein, Juan Valle, Phillip Banks, Pablo Lapuerta, Arthur Sands, Brian Zambrowicz, Douglas Fleming, and Bertram Wiedenmann

*15 Patients*  
*Dose Titration in each Patient*  
*12-Week Treatment*

## Lessons from Phase 2

- Both 250 mg and 500 mg doses deserved further study
- Fewer visits and tests would be reasonable in Phase 3
- Bowel movement frequency is a precise measure
  - Daily reports provide a lot of information
    - But we need to support the interpretation of results

# Interviewing Patients from the Phase 2 Study

## Patient-Reported Symptom Experiences in Patients With Carcinoid Syndrome After Participation in a Study of Telotristat Etiprate: A Qualitative Interview Approach

Heather L. Gelhorn, PhD<sup>1</sup>; Matthew H. Kulke, MD<sup>2</sup>; Thomas O'Doriso, MD<sup>3</sup>;  
Qi M. Yang, PhD<sup>4,\*</sup>; Jessica Jackson, BS<sup>4,\*</sup>; Shanna Jackson, MBA<sup>4</sup>;  
Kristi A. Boehm, MS<sup>4</sup>; Linda Law, MD<sup>4,†</sup>; Jacqueline Kostelec, BA<sup>1,‡</sup>;  
Priscilla Auguste, MHS<sup>1,§</sup>; and Pablo Lapuerta, MD<sup>4</sup>

*A Reduction of 30% or more  
in Bowel Movement Frequency  
is Clinically Meaningful*

# Important Decisions: Advancing to Phase 3

- How many studies?
- How big should they be?
- How can we recruit effectively?

*Telotristat Phase 3 Plan Initiated in 2012*

# The Phase 3 Plan

*At least 120 patients*



*At least 60 patients*



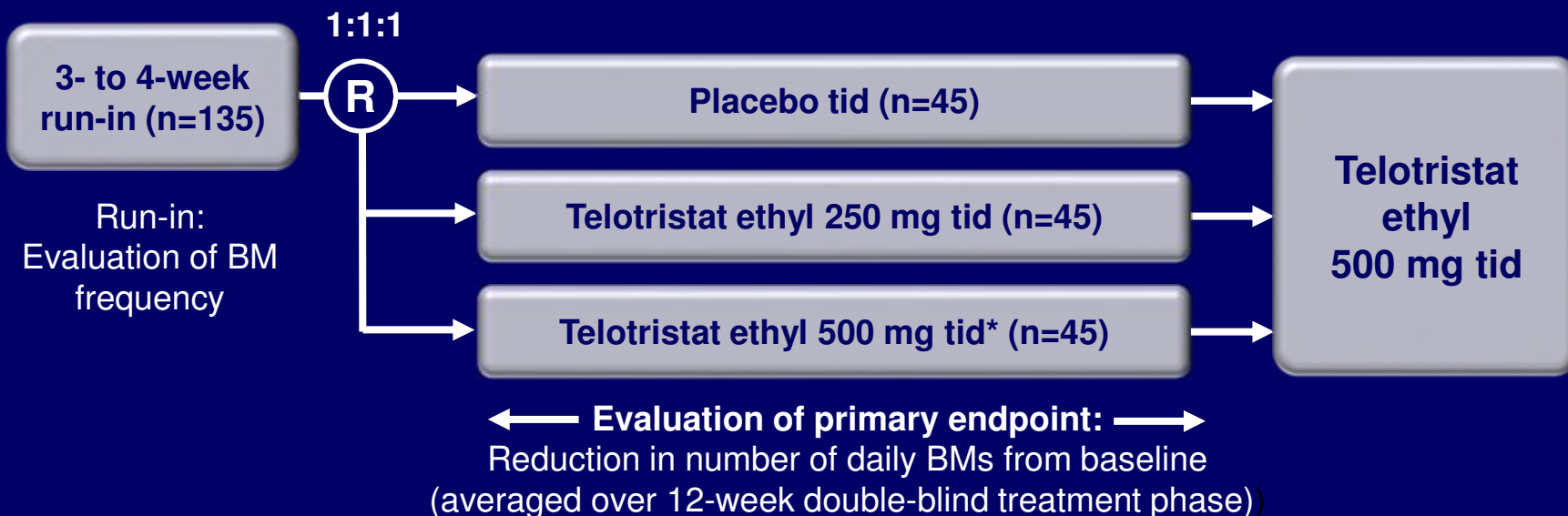
12 Weeks Placebo Control  
+ 36 Weeks Open-Label  
Treatment



PHASE 2 PATIENTS



# TELESTAR: Phase 3 Study Design<sup>1</sup>



All patients required to be on SSA at enrollment and continue SSA therapy throughout study period

Antidiarrheal agent use (eg, loperamide) and rescue short-acting Sandostatin<sup>®</sup> (octreotide) use were allowed while on study<sup>2</sup>

BM=bowel movement; tid=three times daily.

1. TELESTAR (telotristat ethyl for somatostatin analogue not adequately controlled carcinoid syndrome). ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT01677910>. Accessed 09/15. Kulke M, et al. Presented at: ESMO. 2015 (abstr 37LBA).

# Keys to Recruitment

- No required scans
- Optional home visits
- Support for travel
- All symptomatic treatments allowed
- All patients offered open-label treatment after 12 weeks
- If you did not qualify for TELESTAR, you might still qualify for TELECAST
  - With the same randomized design

# Recruitment Results

- Almost 1 year to initiate a significant number of sites
- Approximately 27 months from 1<sup>st</sup> patient to last enrolled
- Sites in US, Canada, France, Italy, UK, Germany, Belgium, the Netherlands, Israel, and Australia
  - 135 patients in TELESTAR
  - 76 patients in TELECAST

# Phase 3 Data Analyses

- Mean change in bowel movement frequency
- Proportions of patients with  $\geq 30\%$  reduction in bowel movement frequency
- Relationship between bowel movement frequency and other symptoms
  - Urgency, consistency, and reports of overall symptom relief
- Different degrees of change (20%, 40%, 60% reductions) and different subgroups (men, women)

Is the change real?

Is it meaningful?

Is it robust?

# Patient Focus: Be Proactive

- Learn about the patient experience early in development
- Use the opportunity to prospectively define clinically meaningful change
  - Who can you identify as a *responder*?
- Discuss responder analyses with FDA prior to phase 3
- Interview *again* in Phase 3
  - Capture the patient voice
  - Support your key efficacy measure
  - Validate your responder analysis

# TELESTAR Patient Exit Interviews: Methods<sup>1</sup>

- Clinical sites in 5 countries invited all TELESTAR patients to be interviewed
  - Australia, Canada, England, Germany, and the United States
- The interview procedure was prespecified in the TELESTAR protocol and approved by ethics committees<sup>2</sup>
- Interview consent was obtained **before initiation of blinded treatment<sup>2</sup>**
- Interviews were conducted by phone between weeks 12 and 14 by an independent expert in patient-reported outcomes<sup>1,2</sup>
- **Patients, clinical sites, and interviewers were blinded to treatment group assignment**

# TELESTAR Patient Exit Interviews: Participant Demographics

	TELESTAR Interview Participants (N=35)	TELESTAR Overall (N=135)
Age, years	62	64
Female, %	51	48
White, %	97	98
Baseline body mass index, kg/m <sup>2</sup>	26	25
Baseline BM frequency, BM/day	5.8	5.7

# Phase 1: Patient Comments About Baseline Symptoms

*“...I was up over 10 [BMs] a day, which wasn't really acceptable...”*

*“...I felt like I was living in my bathroom all the time.”*

*“Uncontrollable diarrhea...where you have to go and there's no stopping it...”*

*“When all I had to do was try to move or walk, and I had to go running to the toilet...”*



# TELESTAR Patient Exit Interviews: Phase 2 – Clinically Meaningful Change

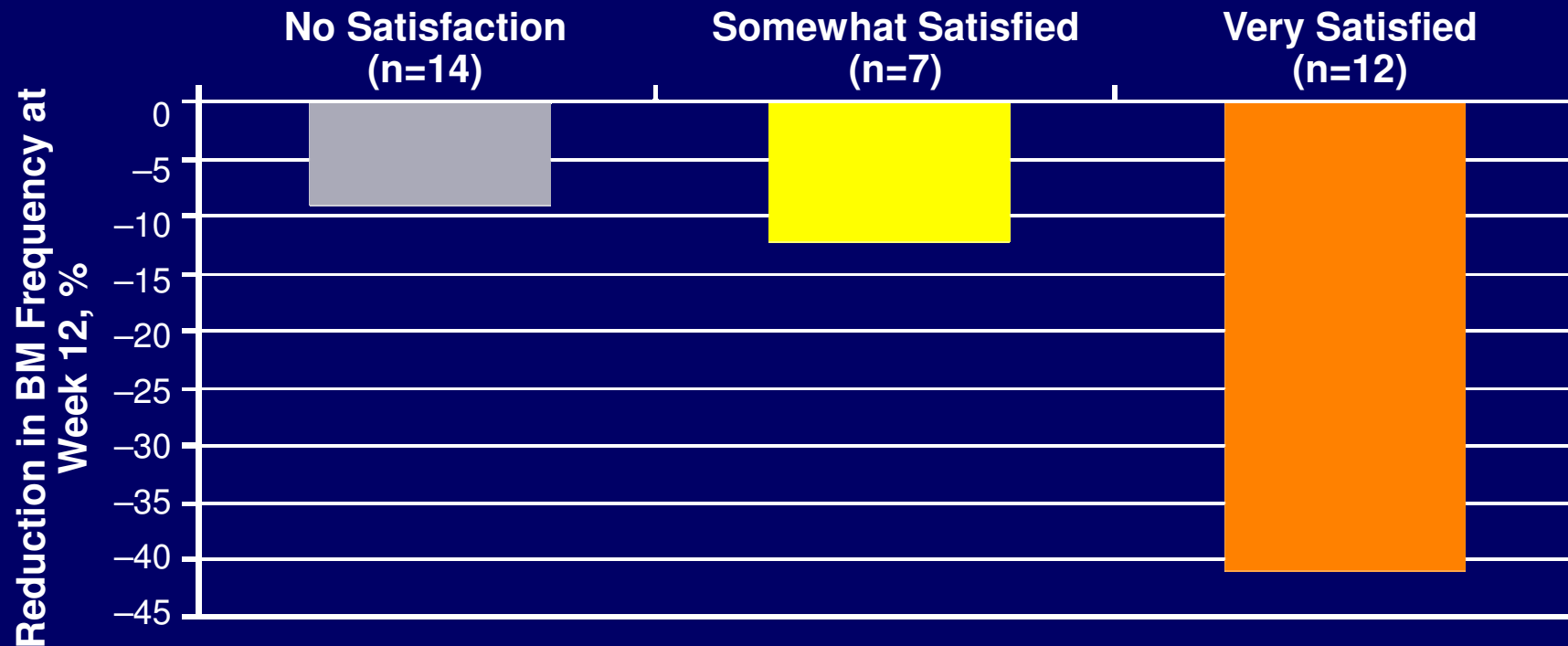
- Participants who reported reductions in BM frequency described better enjoying life, leaving the house, and participating in social and other activities:

*“I definitely feel like I'm not a prisoner in my house, staying 10 feet to the nearest bathroom. I can go out to activities...”*

*“But the biggest change is not having to run to the toilet constantly... You can't live going 20 times a day. I was able to go out more often...”*

- Most participants reported that a BM frequency reduction of at least 30% would be considered meaningful

# TELESTAR Patient Exit Interviews: Phase 2 – Satisfaction and Observed Reduction in BM Frequency at Week 12<sup>1</sup>



Note: Treatment satisfaction reported in question 3. BMs reported daily on electronic diaries during TELESTAR. N=33 from pooled treatment arms.\* Patients who answered 3, 4, or 5 to the treatment satisfaction question were grouped into category “no satisfaction.”

\*Of 35 participants, 2 did not answer the satisfaction question due to early termination or scheduling issue.<sup>2</sup>

1. Anthony L, et al. Poster. NANETS. 2015 (abstr C1) 2. Data on file. Lexicon Pharmaceuticals, Inc.

# TELESTAR Patient Exit Interviews: Conclusions

- The primary endpoint of TELESTAR, a reduction in BM frequency, was very meaningful to patients
- Effective reduction in BM frequency led to improvement in emotional well-being and social and physical function

# Analyzing Safety

- TELESTAR provided placebo-controlled safety data on 135
- TELECAST provided placebo-controlled safety data on 76 patients
- TELEPATH has open-label safety data for up to 6 years of treatment
- A recent safety update (based on continuing safety experience) was provided to FDA

*Control of carcinoid syndrome  
is relevant to the safety of patients*

# Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome

Matthew H. Kulke<sup>1</sup>, Dieter Hörsch<sup>2</sup>, Martyn E. Caplin<sup>3</sup>, Lowell B. Anthony<sup>4</sup>, Emily Bergsland<sup>5</sup>, Kjell Öberg<sup>6</sup>, Staffan Welin<sup>6</sup>, Richard R.P. Warner<sup>7</sup>, Catherine Lombard-Bohas<sup>8</sup>, Pamela L. Kunz<sup>9</sup>, Enrique Grande<sup>10</sup>, Juan W. Valle<sup>11</sup>, Douglas Fleming<sup>12</sup>, Pablo Lapuerta<sup>13</sup>, Phillip Banks<sup>13</sup>, Shanna Jackson<sup>13</sup>, Brian Zambrowicz<sup>13</sup>, Arthur T. Sands<sup>13</sup>, and Marianne Pavel<sup>14</sup>

<sup>1</sup>Dana-Farber Cancer Institute, Boston, Massachusetts, USA, <sup>2</sup>Zentralklinik Bad Berka, Bad Berka, Germany, <sup>3</sup>Royal Free Hospital, London, UK, <sup>4</sup>University of Kentucky, Lexington, Kentucky, USA, <sup>5</sup>UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California, USA, <sup>6</sup>Uppsala University, Uppsala, Sweden, <sup>7</sup>Icahn School of Medicine at Mount Sinai, New York, New York, USA, <sup>8</sup>Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France, <sup>9</sup>Stanford University, Palo Alto, California, USA, <sup>10</sup>Hospital Universitario Ramón y Cajal, Madrid, Spain, <sup>11</sup>The University of Manchester/ The Christie NHS Foundation Trust, Manchester, UK, <sup>12</sup>Ipsen BioScience, Cambridge, Massachusetts, USA, <sup>13</sup>Lexicon Pharmaceuticals, Inc., The Woodlands, Texas, USA, <sup>14</sup>Charité–Universitätsmedizin, Berlin, Germany

# Filing for New Drug Approval

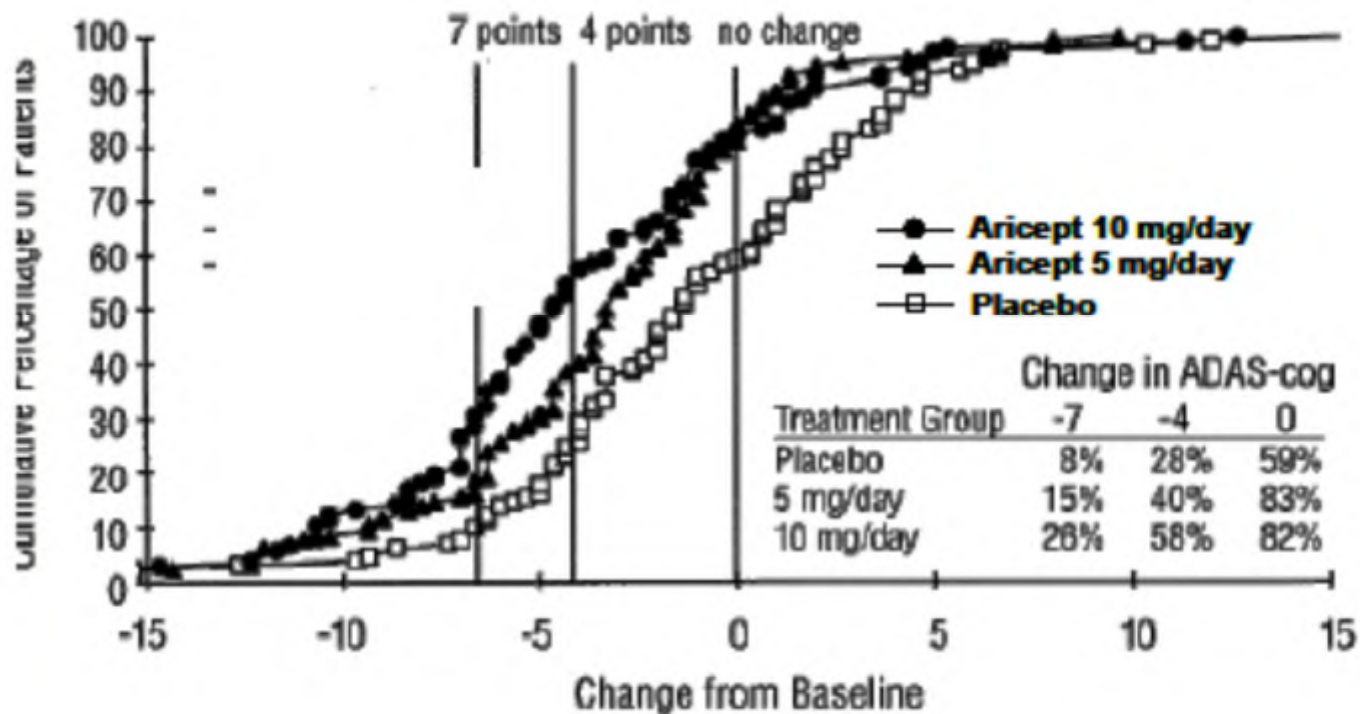
- TELESTAR
- TELECAST
- TELEPATH
- Two Phase 2 studies
- Compassionate use experience
- Several studies in healthy volunteers
- Animal safety data
- Important data on chemistry and manufacturing

# Next Steps

- FDA is evaluating the efficacy and safety of telotristat ethyl
- FDA decision is anticipated by February 28<sup>th</sup>, 2017
- If approved, a product label will be provided

Indications and Usage	Use in Specific Populations
Dosage and Administration	Clinical Pharmacology
Contraindications	Nonclinical Toxicology
Warnings and Precautions	Clinical Studies
Adverse Reactions	Storage and Handling
Drug Interactions	Patient counseling

# Example of an FDA Label: ARICEPT





# Summary

- Clinical development of new treatment for carcinoid syndrome is an extensive process
- Its advancement is based on attention to three main areas

