Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis

Public Meeting – Afternoon Session

September 13, 2018

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Welcome and Introduction

Why are we here this afternoon?

The prospect of new treatments designed for slowing/stabilising hATTR offers significant hope to patients and their families. This is especially so given the context of the disease being hereditary, the negative impact it has on patients and carers' quality of life, and there being no other licensed alternatives available with which to treat the disease.

~ *Amyloidosis Research Consortium*

Working for a private company that is self-insured does not give me unlimited access to funds. We will play this out to whatever our insurance carrier can provide and see what is left. If my portion becomes an amount that starts eroding my ability to care for my family, I will have no choice but to discontinue and eventually enter palliative care. My life insurance along with other provisions I have made will hopefully carry them to the end of their natural life.

~ *Amyloidosis Patient*

Welcome and Introduction

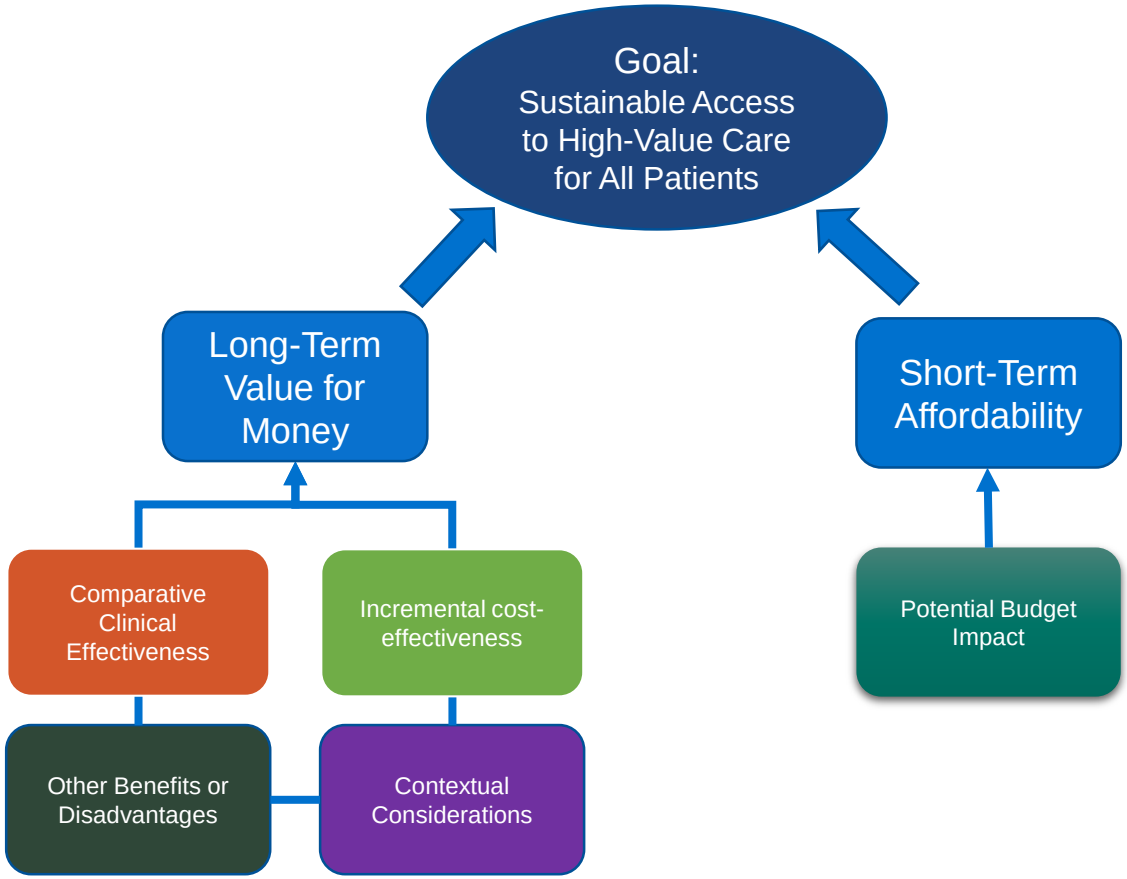
Why are we here this afternoon?

- Increasing health care costs affecting individuals, state and federal budgets
- New treatments for ultra-rare conditions often raise questions about long-term safety and efficacy, appropriate use, and affordability
- Patients can have difficulty accessing drugs
  - High out-of-pocket costs
  - Limited access to treatment centers and experts
- Need for objective evaluation and public discussion of the evidence on effectiveness and value

Welcome and Introduction

How was the ICER report on inotersen and patisiran developed?

- Scoping with guidance from patient groups and advocates, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis, with expertise from Boston Medical Center
- University of California, Davis cost-effectiveness modeling
- Public comment and revision
- Expert reviewers for the evidence report:
  - Merrill D. Benson, MD, Indiana University School of Medicine
  - John L. Berk, MD, Boston Medical Center
  - Rita Faria, MSc, University of York
  - Sarah Richard, Amyloidosis Research Consortium
  - Frederick L. Ruberg, MD, Boston Medical Center
- How is the evidence report structured to support CEPAC voting and policy discussion?


Goal:
Sustainable Access to High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Afternoon Agenda

12:45 pm: Welcome and Opening Remarks

1:00 pm: Presentation of the Evidence and Economic Modeling

- Karen E. Lasser, MD, MPH, Boston Medical Center
- Jeffrey S. Hoch, PhD, University of California, Davis

2:00 pm: Public Comments

2:45 pm: MW CEPAC Vote on Clinical Effectiveness and Value

3:45 pm: Policy Roundtable Discussion

4:45 pm: Reflections from Experts and MW CEPAC Panel

5:00 pm: Meeting Adjourned

Evidence Review

Karen E. Lasser, MD, MPH

Professor of Medicine

Boston Medical Center

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Key review team members:

Kristin Mickle, MPH

Aqsa Mugal

Disclosures:

We have no conflicts of interest relevant to this report.

Hereditary transthyretin amyloidosis (hATTR)

- One of 130 gene mutations that causes protein made in liver to mis-fold and deposit
- Proteins disrupt the function of major organs
- Age of onset/clinical presentation varies
- Cardiac-predominant illness: most predictive of early death
- Neuropathy-predominant illness: most physically disabling, rare worldwide and in US

Therapies for hATTR

- Until recently, no therapy approved in US
- Remove source of transthyretin (TTR) protein
  - Liver transplant
- Stabilize TTR
  - Off-label use of diflunisal
- "Knock down" TTR levels by interfering with RNA
  - Inotersen-SQ- FDA approval expected 10/2018
  - Patisiran-IV+ steroid-FDA approved 8/2018

What we heard from patients

- Severe disabling illness that profoundly impacts all aspects of quality of life
- Affects multiple members and generations of families
- Difficult for patients to travel to centers of excellence to receive treatment
- New treatments for hATTR offer much-needed hope to patients and their families
- Affordability of new therapies is a major concern

Scope of the Review

- To evaluate the clinical effectiveness of inotersen and patisiran, respectively, for hATTR
- Comparator: Best supportive care

Outcomes
Neurologic impairment
Quality of life
Cardiac outcomes
Disease progression
Functional impairment
Harms
Mortality

Body of Evidence

- Two trials of inotersen
  - 1 Phase III RCT with open label extension (OLE), 1 single-arm, open-label trial
- Two trials of patisiran
  - 1 Phase III RCT, 1 Phase II trial, and OLE

Overview of Randomized Trials

Key Trials	Treatment Groups	Patient Characteristics	Primary Outcome
NEURO-TTR Phase III Parallel-arm RCT 15 months	Placebo Inotersen	N=173 Mean age: 59 92% white 48% US 67% FAP stage 1	Modified Neuropathy Impairment Score+7 (Ionis)-347 points Norfolk Quality of Life–Diabetic Neuropathy questionnaire
APOLLO Phase III Parallel-arm RCT 18 months	Placebo Patisiran	N=225 Median age: 62 76% white 20% US 46% FAP stage 1	Modified Neuropathy Impairment Score+7-304 points

Primary clinical outcomes

- Modified Neuropathy Impairment Score+7
  - Composite score: motor strength, reflexes, sensation, nerve conduction, autonomic function
  - Higher score = worse neurologic function

- Norfolk Quality of Life–Diabetic Neuropathy questionnaire
  - Higher score = poorer quality of life

Secondary and exploratory outcomes

- Modified BMI
  - Used to measure wasting associated with progression of neuropathy and disability
- Disease progression
  - Familial Amyloid Polyneuropathy (FAP) stage
    - Three-stage measure from 1 (ambulate without assistance) to 3 (wheelchair or bedridden)
  - Polyneuropathy disability score (PND)
    - Five-stage measure from 0 (no impairment) to 4 (wheelchair or bedridden)
- Cardiac
  - N-terminal pro-BNP
  - Echocardiographic measures

Results: Inotersen

Co-primary outcome: change in mNIS+7

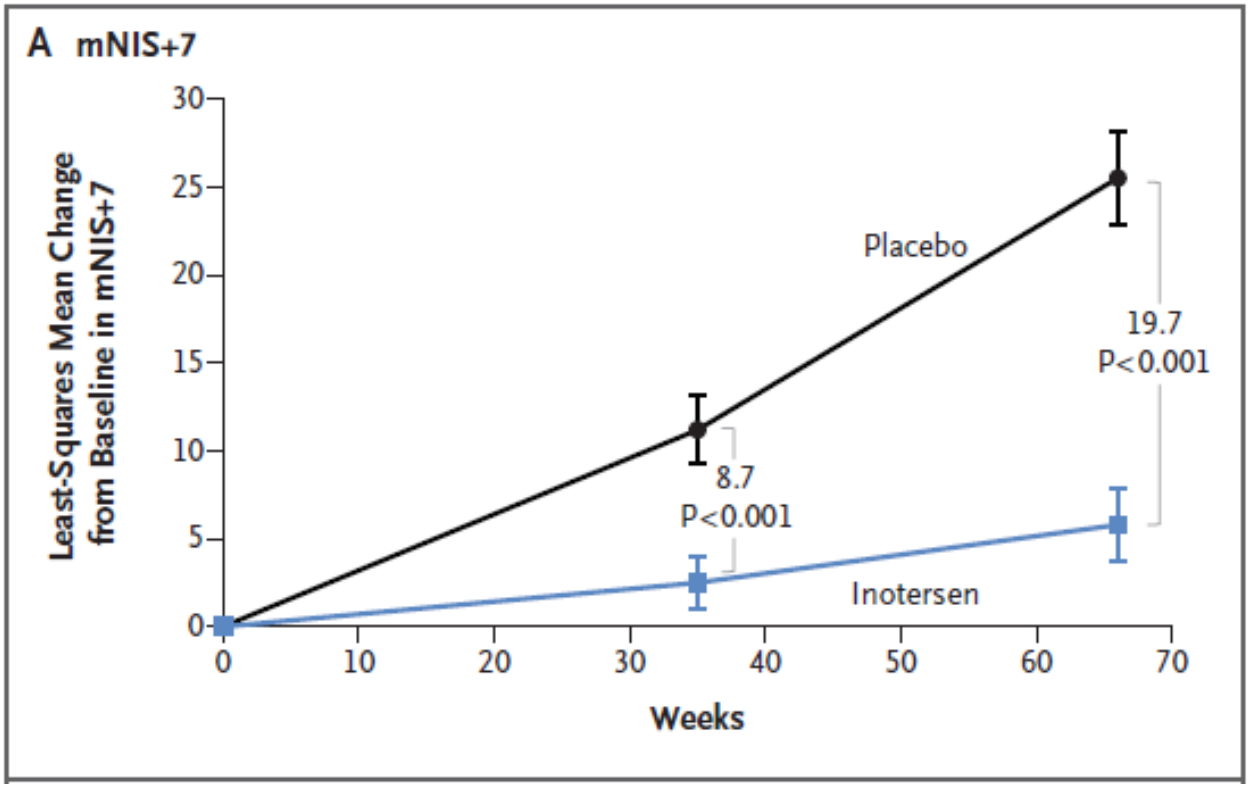


Figure 4 Least Squares mean Change from Baseline in mNIS+7. Adapted from *Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis* by Benson et al, 2018. Retrieved from https://www.nejm.org/doi/10.1056/NEJMoa1716793

Co-primary outcome: change in QOL

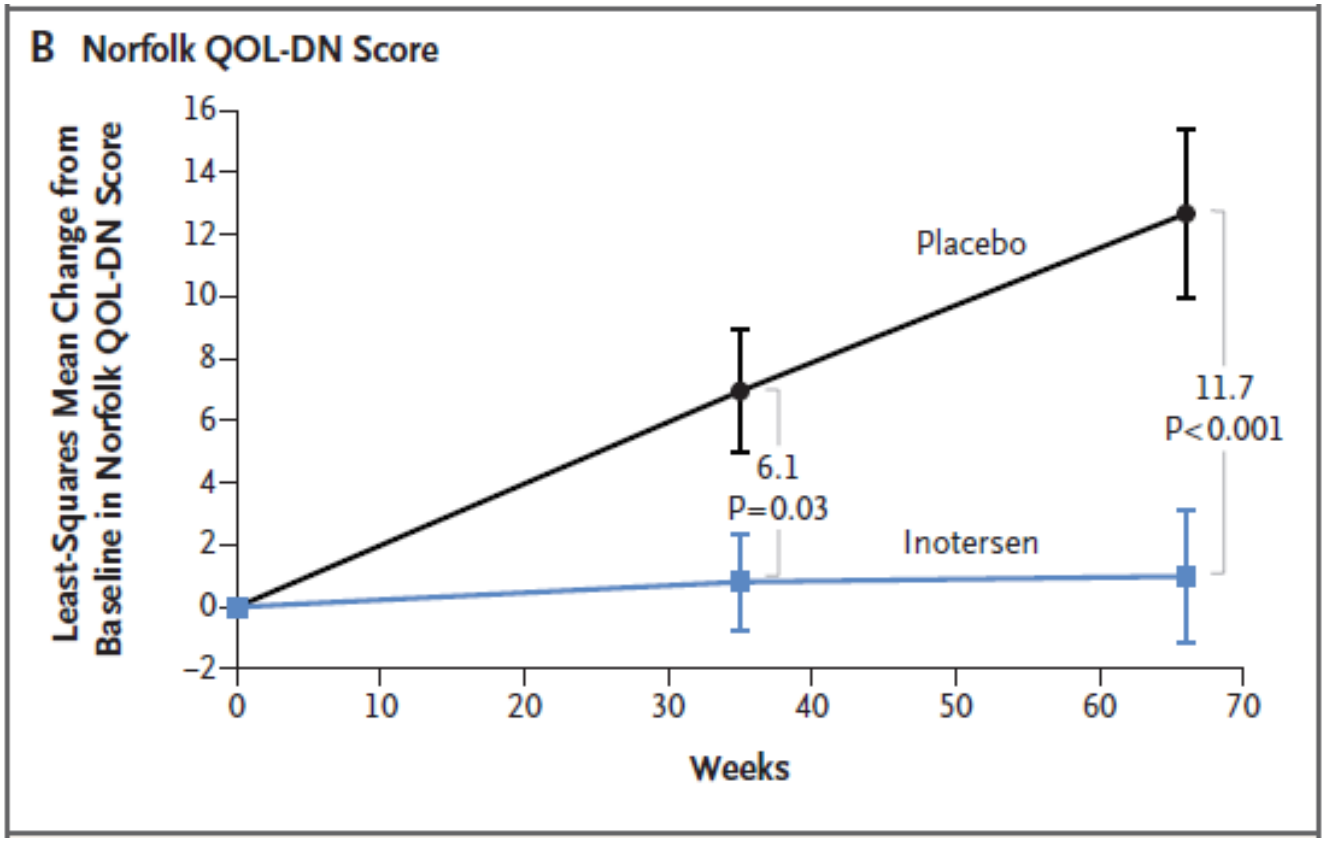


Figure 2 Least Squares mean Change from Baseline in Norfolk QOL-DN Score Adapted from *Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis* by Benson et al, 2018. Retrieved from https://www.nejm.org/doi/10.1056/NEJMoa1716793

Secondary Outcomes-Inotersen

- Polyneuropathy disability score
  - No difference between inotersen and placebo
- Cardiac
  - No improvement in echocardiographic measures
- Modified BMI
  - No significant differences in mBMI vs. placebo

Harms, n (%)-Inotersen

	Placebo (n=60)	Inotersen (n=112)
Any AE leading to DC	1 (2)	16 (14)
Any serious AE	13 (22)	36 (32)
Death	0	5 (4)
Glomerulonephritis	0	3 (3)
Thrombocytopenia	1 (2)	15 (13)
Anti-inotersen antibodies	NR	34 (30)

Results: Patisiran

Primary outcome: change in mNIS+7

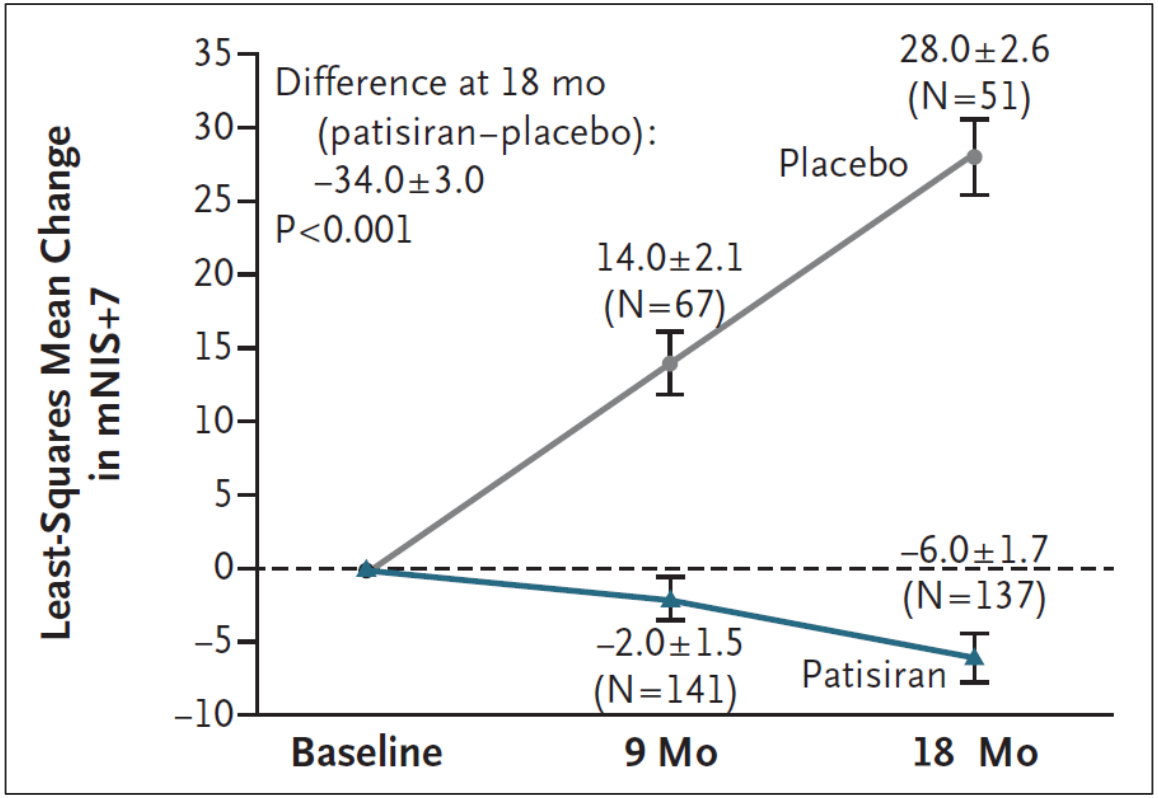


Figure 3 *Least Squares Mean Change in mNIS+7.* Adapted from *Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis* by Adams, et al 2018, retrieved from https://www.nejm.org/doi/10.1056/NEJMoa1716153

Secondary outcome: change in QOL

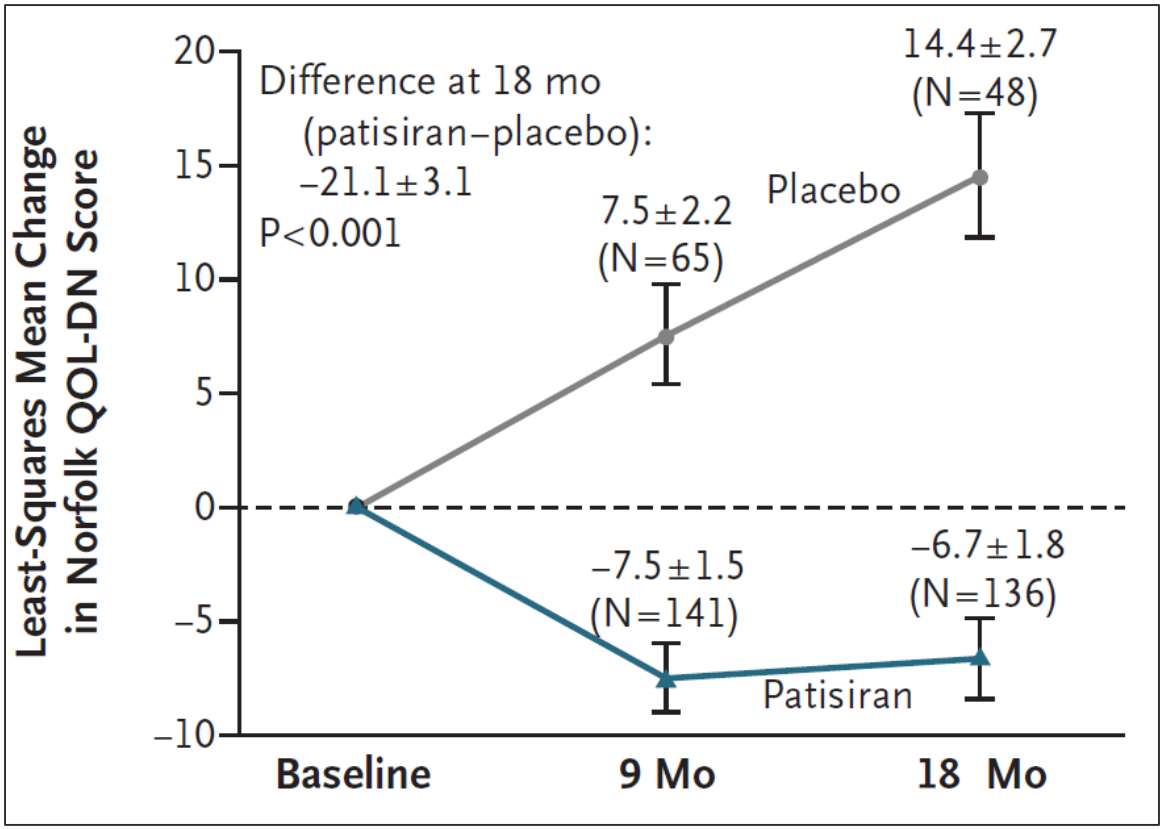


Figure 4 Least-Square Mean Change in Norfolk QOL-DN Score. Adapted from *Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis* by Adams, et al 2018, retrieved from https://www.nejm.org/doi/10.1056/NEJMoa1716153

Secondary Outcomes-Patisiran

- Modified BMI
  - Improved vs. placebo
- Familial Amyloid Polyneuropathy stage
  - Stable or improved vs. placebo
- Polyneuropathy Disability Score
  - Stable or improved vs. placebo
- Cardiac
  - NT-proBNP decreased vs. placebo; unclear clinical significance
  - Post-hoc analyses

Harms, n (%)-Patisiran

	Placebo (n=77)	Patisiran (n=148)
Any AE leading to DC	11 (14)	7 (5)
Any serious AE	31 (40)	54 (36)
Death	6 (8)	7 (5)
Peripheral edema	17 (22)	44 (30)
Infusion reactions	7 (9)	28 (19)

Harms-Patisiran

Low-moderate risk long-term harm from concomitant steroid administration

- Depends on patient characteristics
- Based on analogous steroid use in other therapeutic areas

Controversies & Uncertainties

- Unknown clinical significance for magnitude of changes
- Not yet possible to determine which patients are likely to respond to treatment
- Studies not powered on cardiac outcomes
  - Limited generalizability to US
- Loss to follow-up in inotersen arm higher
- Long-term safety unknown
  - Patisiran is the first RNAi therapeutic approved by the US FDA

ICER Evidence Ratings

	ICER Evidence Rating
Inotersen vs. Placebo	Comparable or better (C+)
Patisiran vs. Placebo	Incremental or better (B+)

Potential Other Benefits and Contextual Considerations

- Patisiran is first US medication approved to treat hATTR, inotersen may follow
- Injectable formulation of inotersen
- New treatments may positively impact caregiver and family burden
- Hope for affected families
- Potential to increase screening and diagnosis

Public Comments Summary

- Initial evidence rating of P/I for inotersen was too low
- Some outcomes that matter most to patients not captured in trials
- Tafamidis: an important new treatment on the horizon
- Important questions that remain: when to initiate therapy, how long to continue

Conclusions

- New therapies appear to halt progression or improve neuropathy symptoms and quality of life in hATTR
- Uncertainty regarding specific safety issues and long-term safety overall
- Studies with primary cardiac endpoints are needed
- Affordability is a major concern for patients and their families

Long-Term Cost-Effectiveness

Jeffrey Hoch, PhD

Professor and Chief, Division of Health Policy and Management

Associate Director, Center for Healthcare Policy and Management

Department of Public Health Sciences

University of California, Davis

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Key Team Members

Lauren Cipriano, PhD, Western University, London, Ontario, Canada

Elise Evers, University of York, York, United Kingdom

Yi Zhang, PhD, University of California, Davis

Kristin Mickle, MPH, Institute for Clinical and Economic Review

Daniel A. Ollendorf, PhD, Institute for Clinical and Economic Review

Rick Chapman, PhD, Institute for Clinical and Economic Review

Disclosures:

Financial support was provided to the University of California, Davis from the Institute for Clinical and Economic Review.

University researchers have no conflicts to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

Objective

- To estimate the incremental cost effectiveness of **inotersen** and **patisiran** in comparison to best supportive care* for hereditary transthyretin amyloidosis from a health care sector (and modified societal) perspective over a lifetime.

*Best supportive care is defined for inotersen as in the NEURO-TTR trial and for patisiran as in the APOLLO trial.

Methods Overview

- **Model:** Markov model
- **Setting:** United States
- **Perspective:** Health care sector (and modified societal) perspectives
- **Time horizon:** Lifetime
- **Discount rate:** 3% per year (costs and outcomes)
- **Cycle Length:** 1 month
- **Primary outcome:** Cost per quality-adjusted life year (QALY) gained
  - **Secondary outcome:** Cost per life year (LY) gained

Base-Case Population (Inotersen)

Cohort Characteristic (Baseline)	Value*
Mean age	59 years
Female	31%
FAP Stage 1	67%
FAP Stage 2	33%
Severe Cardiac Involvement (NT-proBNP > 3,000)	14.2%

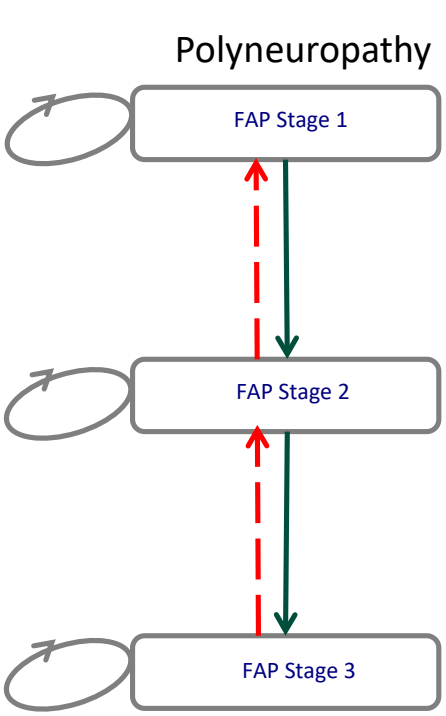
*All from NEURO-TTR, except the 14.2% assumption based on the relative frequency of general cardiac sub-populations in the NEURO-TTR (inotersen) and the APOLLO trials (patisiran)

Base-Case Population (Patisiran)

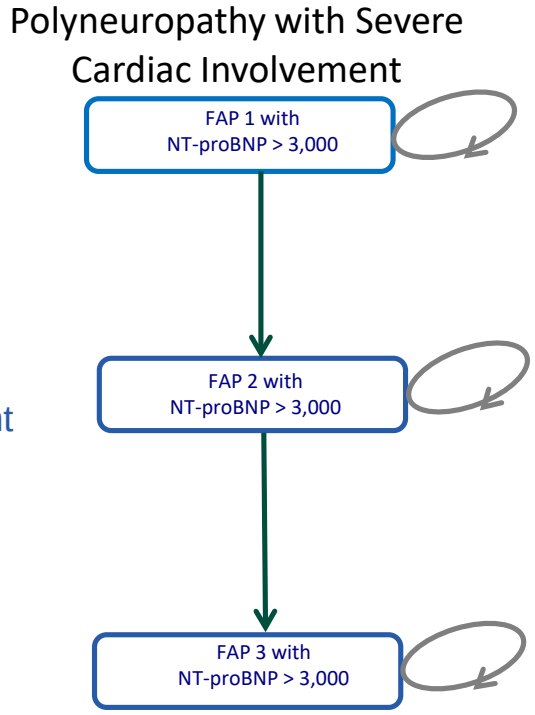
Cohort Characteristic (Baseline)	Value*
Mean age	62 years
Female	26%
FAP Stage 1	46%
FAP Stage 2	54%
Severe Cardiac Involvement (NT-proBNP > 3,000)	12%

*All from the APOLLO trial

Model Schematic



1) Improvement possible
2) Death (from all states)
3) Severe Cardiac Involvement



Key Assumptions

- Patients do not undergo liver transplantation.
  - Infrequent use; unclear impact
- Some quality of life utility benefit for new treatments within the same FAP stage
  - Difference in Norfolk QoL does not match large % with “no change” in FAP Stage progression
- Patients stay on treatment until drug discontinuation.
  - Assumed numbers match that seen in the respective trials.

Key Parameters: Cost Inputs

- Drug cost: $345,000 per year (net expected price)
- Plus annual costs of
  - Inotersen:
    - Training visit for first injection ($74)
  - Patisiran:
    - 4.3% markup ($14,835)
    - Infusion administration ($3,965)
    - Pre-infusion drugs ($50)
- Office visits, ED visits, hospitalization costs from Medicare fee schedule
- Stage-specific annual costs of caregiving
  - including disease-related acute events and treatment costs

Key Parameters: Health Utilities

Health State	Utility Value if NT-proBNP ≤ 3,000
FAP Stage 1	0.710
FAP Stage 2	0.570
FAP Stage 3	0.170

Patients with:
Severe cardiac involvement incur an additional 10% loss of utility;
New treatment incur 0.05 to 0.14 more utility (depending on stage and drug)

Key Parameters: Mortality

- 3 different death rates incorporated:
  - "Natural" age-specific death rate (matches trials' Female/Male ratio)
    - US Life tables
  - "FAP stage" death rate
    - Swiecicki et al. (2015)
  - "Severe cardiac involvement" death rate
    - Slama et al. (2018)

Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. Amyloid. 2015;22(2):123-131.

Slama M, Solomon S, Adams D, et al. Analysis of NT-proBNP Baseline Levels in APOLLO as a Predictor of Survival in Hereditary Transthyretin-Mediated (hATTR) Amyloidosis. European Society of Cardiology Heart Failure 2018 Congress; May 26 -29, 2018. Vienna, Austria.

INOTERSEN Results

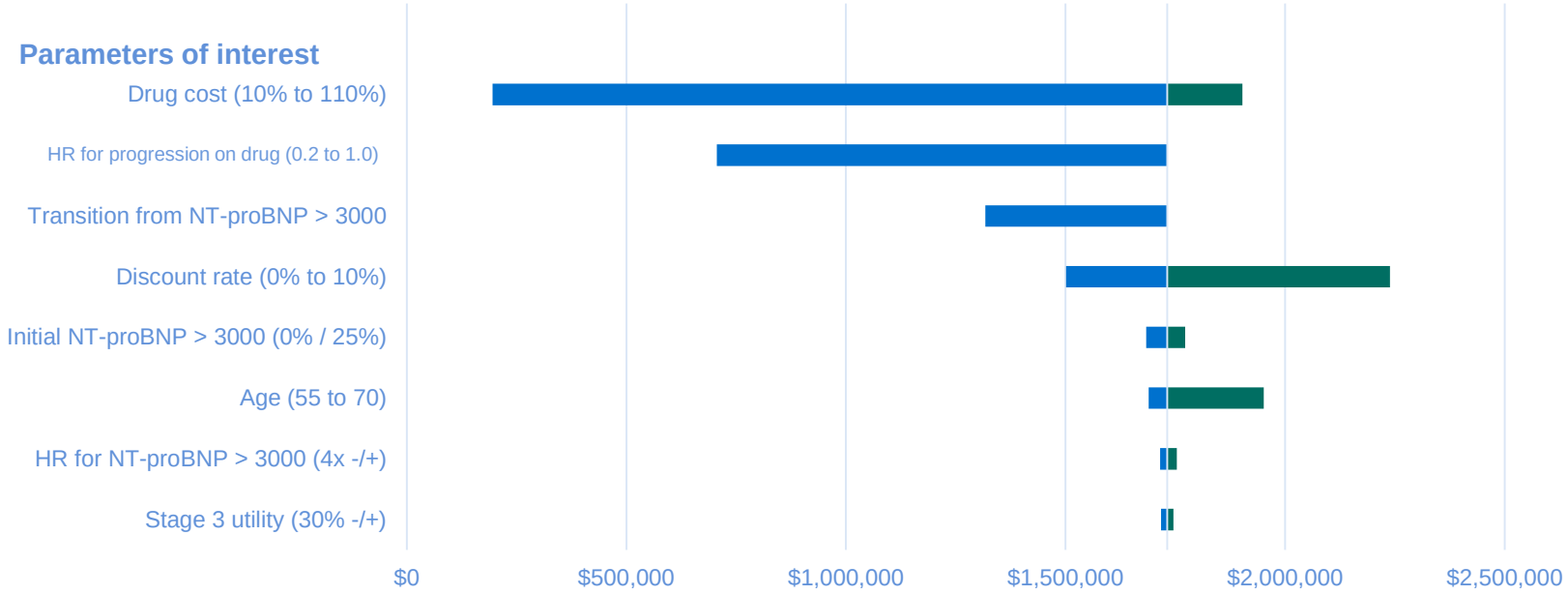
Inotersen Results: Total Cost and QALYs

	3% Discount Rate	
	Total Costs	QALYs
Health Care Sector Perspective		
Inotersen	$1,510,000	4.54
Best Supportive Care	$330,000	3.86

Inotersen Results (Continued, 3% Discount Rate)

How much more?	Inotersen vs. Best Supportive Care
Incremental Costs	
Health Care Sector Perspective	$1,180,000
Incremental Outcomes	
QALYs	0.68 QALYs
Incremental Cost-Effectiveness Ratio (QALYs)	
Health Care Sector Perspective	$1,730,000 per QALY

One-Way Sensitivity Analyses: Inotersen, Health Care Sector Perspective



Base case incremental cost-effectiveness ratio: $1,730,000 per QALY gained

PATISIRAN Results

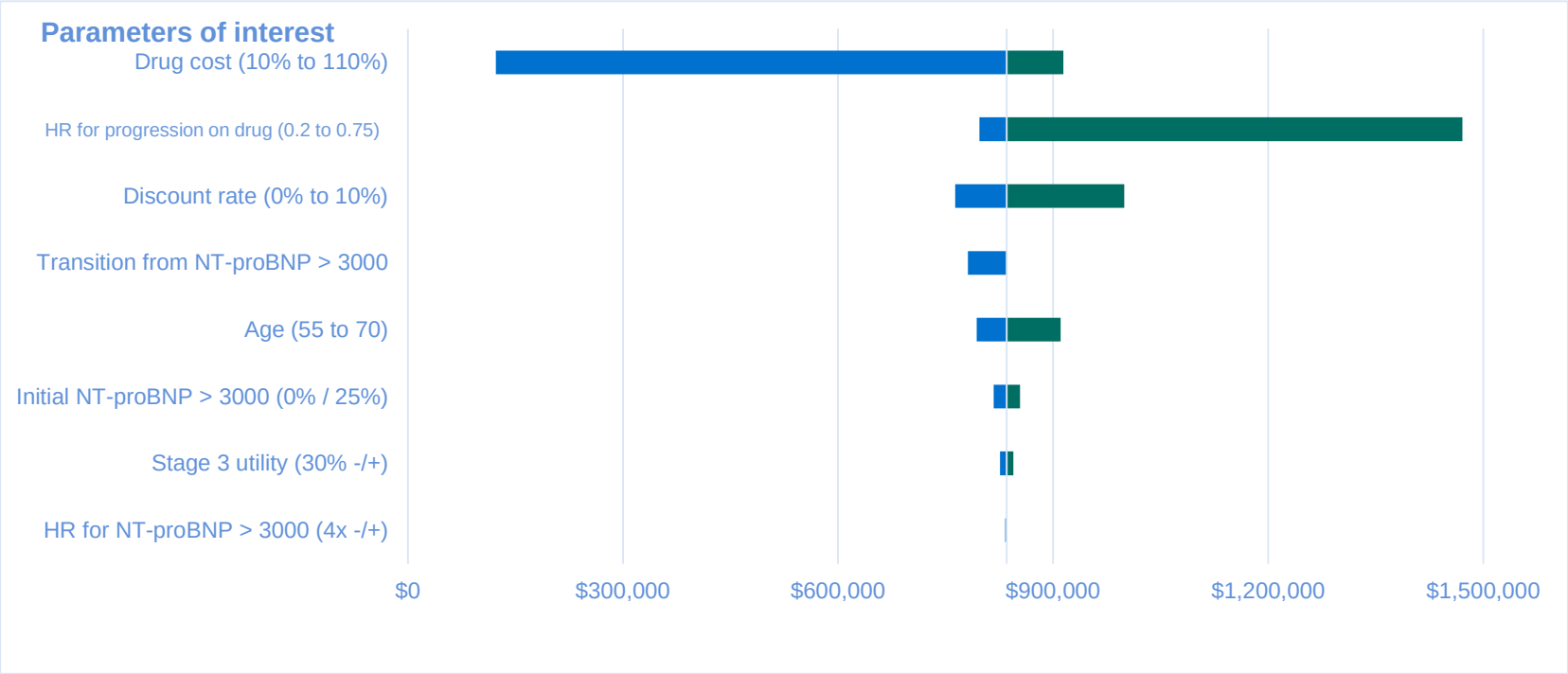
Patisiran Results: Total Cost and QALYs

	3% Discount Rate	
	Total Costs	QALYs
Health Care Sector Perspective		
Patisiran	$3,170,000	6.54
Best Supportive Care	$310,000	3.11

Patisiran Results (Continued, 3% Discount Rate)

How much more?	Patisiran vs. BSC
Incremental Costs	
Health Care Sector Perspective	$2,860,000
Incremental Outcomes	
QALYs	3.43 QALYs
Incremental Cost-Effectiveness Ratio (QALYs)	
Health Care Sector Perspective	$835,000 per QALY

One-Way Sensitivity Analyses: Patisiran, Health Care Sector



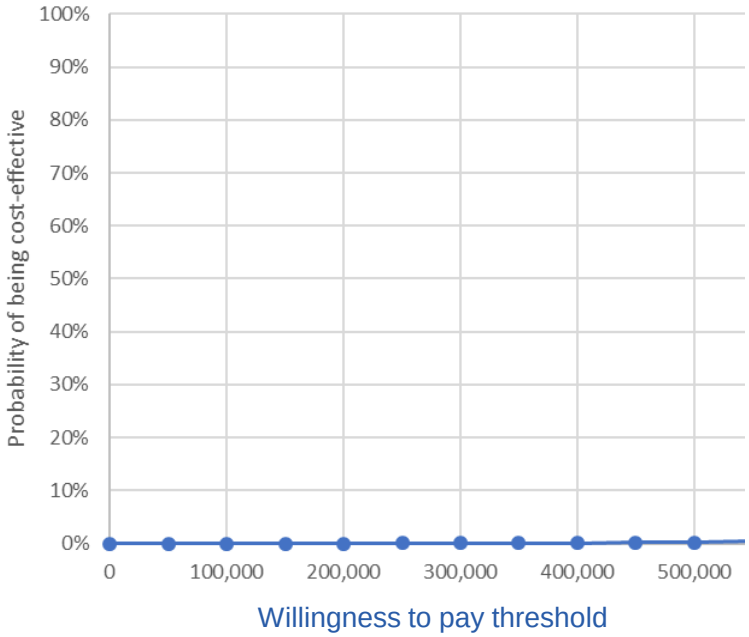
Base case incremental cost-effectiveness ratio: $835,000 per QALY gained.

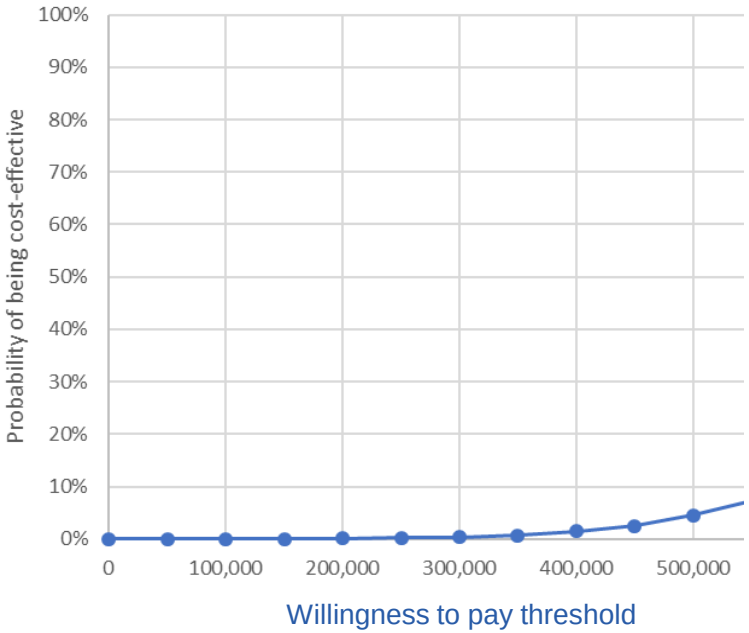
Scenario Analyses for Both Treatments

- Different utilities
  - Prior UK model's utilities (↑)
  - Worst utilities reported in the literature (↑)
  - No utility bonus within FAP Stage (↑)

- Different health care costs
  - Double costs (↑)
  - Half costs (↓)

Cost-Effectiveness Acceptability Curves (CEACs) for Inotersen and Patisiran





Results from probabilistic sensitivity analysis

Limitations

- Lack of relevant cost-effectiveness data; modeling points out where the uncertainty matters
- Lack of long-run clinical evidence on discontinuation, benefits, and risks from using new treatments; role for more evidence
- Differences in trials make direct comparison not feasible

Public Comments

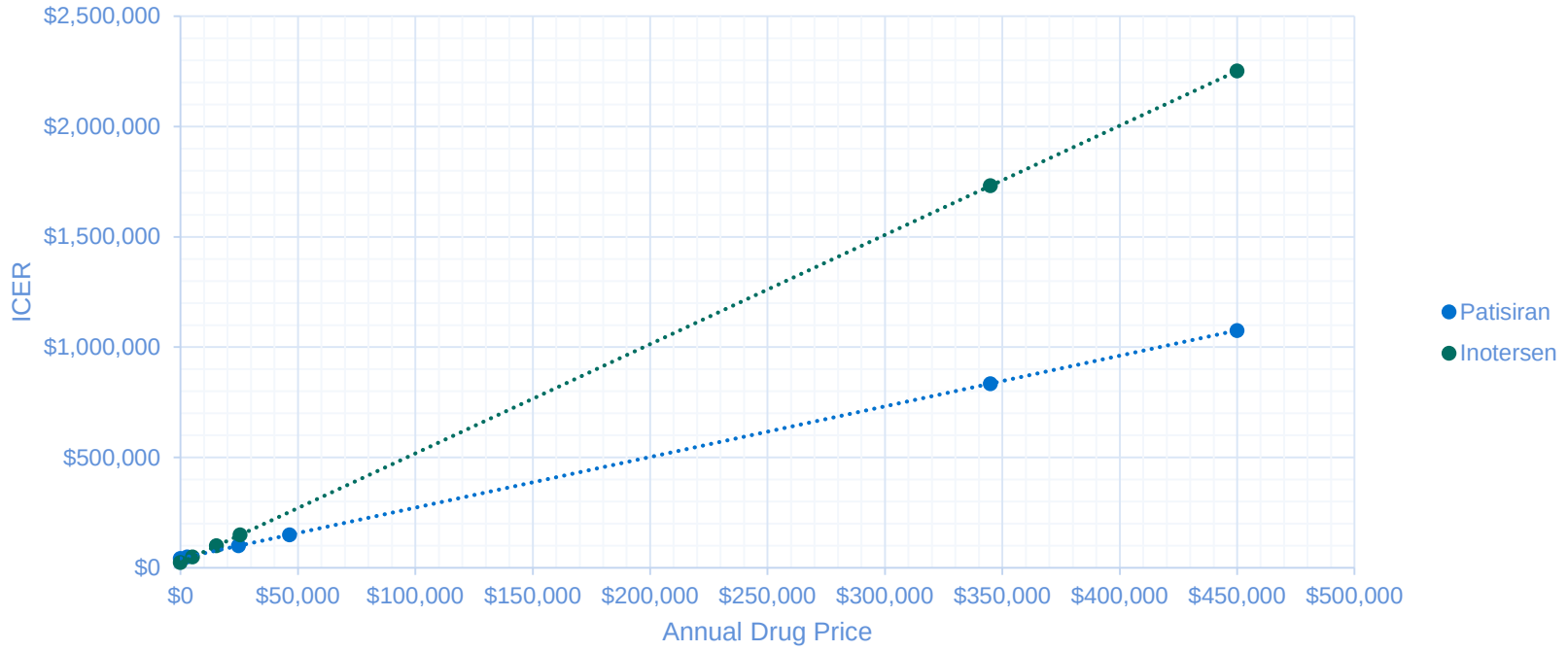
- Allow for “benefit” in quality of life even *within* FAP Stage (plateau)
- Consider liver transplant
- Explore impact on caregivers
- Keep analysis of the new treatments separate

Conclusions from the Cost-Effectiveness Analysis

- The estimated cost-effectiveness of **inotersen** is not near commonly used cost-effectiveness thresholds.
- The estimated cost-effectiveness of **patisiran** is not near commonly used cost-effectiveness thresholds.
- For treatments for ultra-rare diseases, policymakers often consider other benefits and contextual considerations that may lead to funding at higher cost-effectiveness thresholds.

Supplemental Slides

Other Results



Public Comment and Discussion

Muriel Finkel

Founder and President, Amyloidosis Support Groups

Conflict of interest:

- Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies

- *Amyloidosis Support Groups is a 501c3 non-profit charity comprised of volunteers.*
- *Amyloidosis Support Groups is largely dependent on donations from the general public, but also receives donations and grants from pharmaceutical companies. In the last year, the group received financial assistance from Bridge Bio (Eidos), Pfizer, Alnylam, Ionis, Akcea, and Prothena. These funds help support the group's annual meeting.*

Charles Horwath
Patient Advocate

Conflict of interest:

- None declared.

Kristen Hsu

Executive Director, Clinical Research, Amyloidosis Research Consortium

Conflict of interest:

- A relationship that could reasonably be considered a financial conflict of interest.

- Over the past year, Amyloidosis Research Consortium (ARC) has received financial support for projects from the following companies: Ionis, Pfizer, Alnylam, Takeda, Janssen, and Prothena. ARC retains all influence, control, and autonomy over projects for which it's received external support.

Dawn Myers
Patient Advocate

Conflict of interest:

- None declared.

Manufacturer Public Comment and Discussion

Speakers

Name	Title	Company
Sonalee Agarwal, PhD	Head, Value & Evidence Strategy	Alnylam
Spencer Guthrie, MPH	Vice President, Global TTR Strategy	Akcea

Voting Questions

WIFI Network: Marriott Guests
Password: 0809

0. The Art Institute of Chicago holds the largest collection of _____ paintings outside the Louvre.

A. Realist
B. Surrealist
C. Impressionist
D. Abstract

Patient Population for all questions:

For each question, we are considering adults with hereditary transthyretin amyloidosis (hATTR).

1. Is the evidence adequate to demonstrate that the net health benefit of inotersen plus best supportive care is superior to that provided by best supportive care alone?

A. Yes

B. No

2. Is the evidence adequate to demonstrate that the net health benefit of patisiran plus best supportive care is superior to that provided by best supportive care alone?

A. Yes

B. No

3. Is the evidence adequate to distinguish the net health benefit between inotersen and patisiran when added to best supportive care?

A. Yes

B. No

4. When compared to best supportive care alone, does the addition of inotersen or patisiran offer one or more of the following “other benefits”?

A. Offers reduced complexity that will significantly improve patient outcomes.

B. Will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.

C. Will significantly reduce caregiver or broader family burden.

D. Offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.

E. Will have a significant impact on improving patients’ ability to return to work and/or their overall productivity.

F. Will have a significant positive impact outside the family, including on schools and/or communities.

G. Will have a significant impact on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.

H. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention: _____

5. Are any of the following contextual considerations important in assessing inotersen's or patisiran's long-term value for money in patients?

A. Intended for the care of individuals with a condition of high severity.

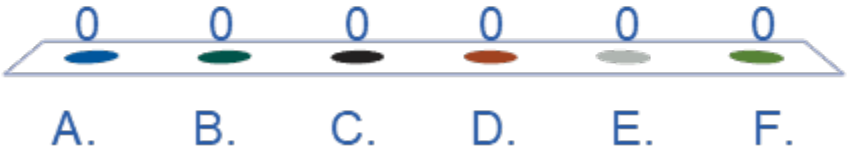
B. Intended for the care of individuals with a high lifetime burden of illness.

C. First to offer any improvement for patients with this condition.

D. Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.

E. Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits.

F. There are additional contextual considerations that should have an important role in judgments of the value of this intervention: _____.

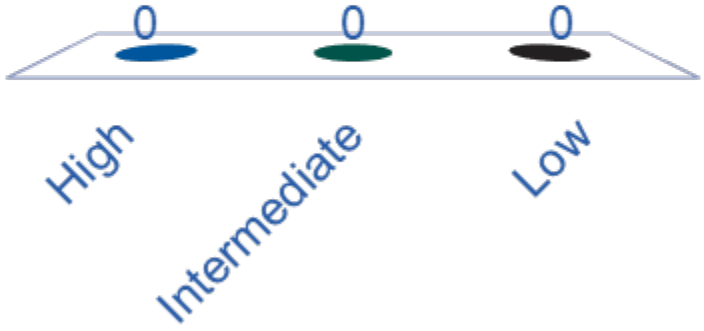


6. For adults with hereditary transthyretin amyloidosis, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of inotersen plus best supportive care compared with best supportive care alone?

A. High

B. Intermediate

C. Low

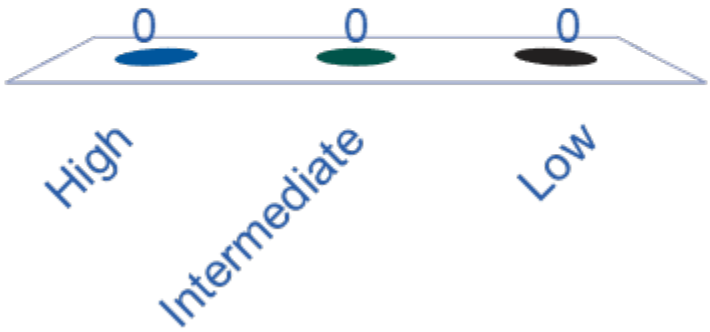


7. For adults with hereditary transthyretin amyloidosis, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of patisiran plus best supportive care compared with best supportive care alone?

A. High

B. Intermediate

C. Low



Policy Roundtable

Policy Roundtable Participants

Name	Title	COI Declaration
John Berk, MD	Associate Professor of Medicine, Amyloidosis Center, Boston University	Study site investigator for clinical trials of diflunisal, inotersen, patisiran, and tafamidis.
Joel Buxbaum, MD	Consulting Chief Medical Officer, Misfolding Diagnostics; Professor Emeritus, Molecular Medicine, The Scripps Research Institute	None declared.
Alan Eisenberg, MPP	Vice President, Global Government Relations & Public Policy, Alnylam Pharmaceuticals	Full-time employee of Alnylam.
Young Fried, PharmD, MSP	Vice President, Pharmacy Plan Services, HealthPartners	Full-time employee of HealthPartners.
Kristen Hsu	Executive Director, Clinical Research, Amyloidosis Research Consortium	Full-time employee of Amyloidosis Research Consortium.
Dustin Kaehr	Director, Leadership Development, Lippert Components; Patient Advocate	None declared.
Michael Pollock	Vice President, Global Market Access, Akcea Therapeutics	Full-time employee of Akcea Therapeutics.

Expert and CEPAC Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on/about October 4
  - Includes description of CEPAC votes, deliberation; policy roundtable discussion
- Materials available at

  https://icer-review.org/topic/amyloidosis/

Adjourn