From Advanced Genetics to Aducanumab…

Navigating the Good, the Bad and the Ugly of the Latest Therapeutic Developments

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Sarah K. Emond, MPP

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This New Treatment Could Save the Lives of Babies. But It Costs $2.1 Million.

The price set by the Swiss drugmaker Novartis may be the world's highest for a single treatment — prompting renewed debate about how society will pay for gene-therapy breakthroughs.

PHARMA

A $3M gene therapy: Bluebird bio breaks its own pricing record with FDA approval of Skysona

By **Angus Liu** • Sep 19, 2022 10:55am

PHARMA

UPDATED: Bluebird bio's $2.8M gene therapy Zynteglo wins FDA backing. Will its US launch take flight?

By **Fraiser Kansteiner** • Aug 17, 2022 01:55pm

Gene Therapy Used to Treat Hemophilia

By Amy Docker Marcus

Updated Dec. 10, 2011 11:20 am ET

INSIGHTS / EDUCATION

No One Really Knows How We'll Pay for Gene Therapies

September 21, 2022 02:59 PM EDT | Cell/Gene Tx

Are $3M gene therapies the new normal? Experts say bluebird will be a test case for a market ready for prime time

Zachary Brennan
Senior Editor

PAYERS

The gene therapy pipeline may be at a 'tipping point.' Here's why Optum says payers need to take notice

By **Paige Minemyer** • Aug 8, 2022 03:37pm

FIRST OPINION

How will we pay for the coming generation of potentially curative gene therapies?

By Bill Cassidy June 12, 2019

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Institute for Clinical and Economic Review (ICER)

- **Independent** health technology assessment group whose reviews are funded by non-profit foundations
- Develop **publicly-available value assessment reports** on medical tests, treatments, and delivery system innovations
- Convene regional independent **appraisal committees** for public hearings on each report
- Use cost-effectiveness analysis to determine **value-based price benchmarks**

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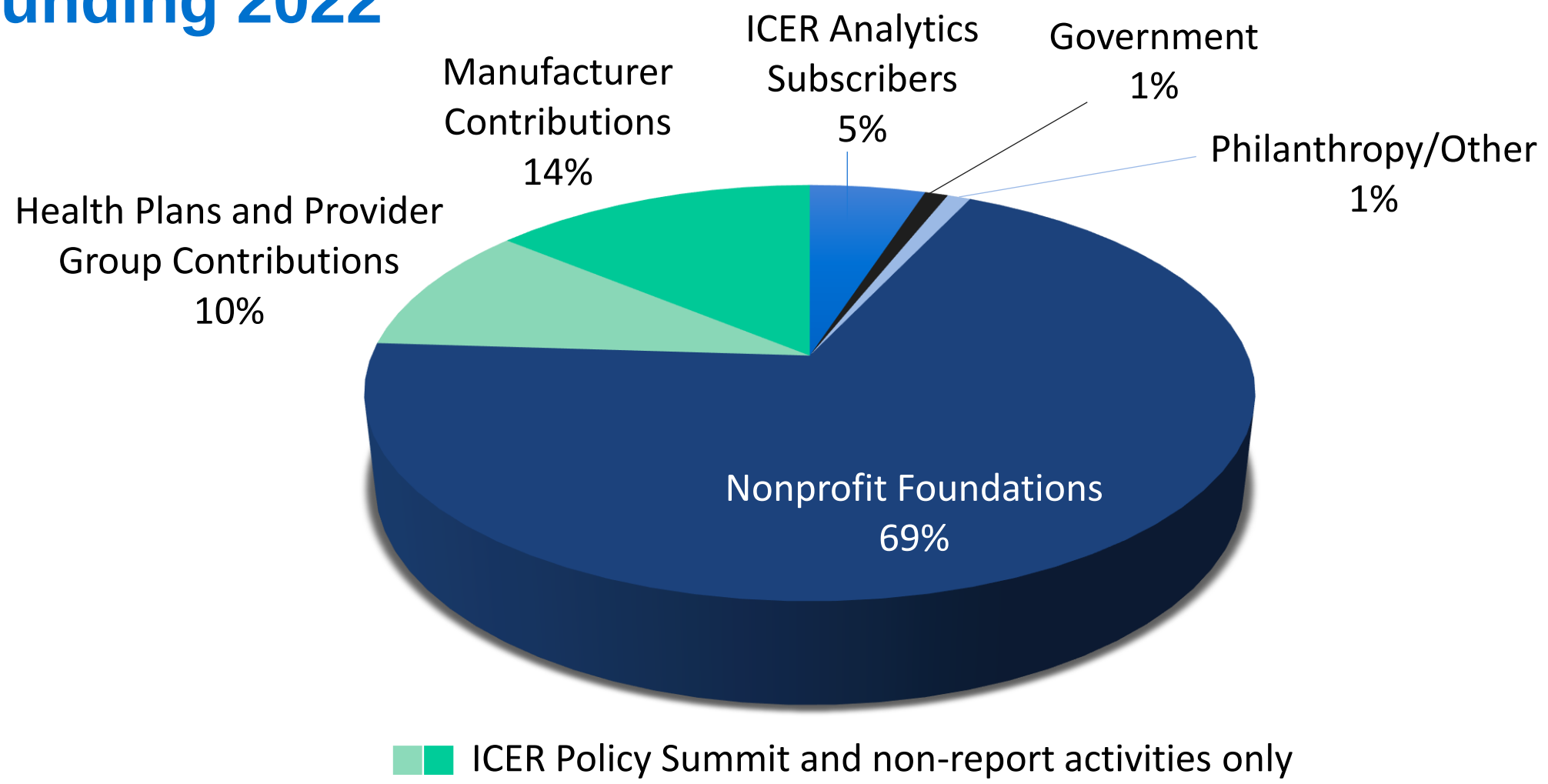
Funding 2022



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Fair Pricing.

Fair Access.

Future Innovation.

Why change is needed

- Amazing advancements in the treatment of serious diseases
- Higher and higher prices, purchasers have limited tools to manage other than restrictive formularies
- Clinicians are frustrated with paperwork, ever-changing list of preferred drugs
- Patients may not get access to appropriate treatment in a timely manner, while premiums and out-of-pocket costs go up

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Why Does the US Need Independent Research?

- FDA approval means “safe and effective”
  - Little comparative data; no consideration of cost or value
- Health systems routinely make tradeoff decisions
  - Asymmetric information, limited time, short-term incentives
- Unlike many countries, no centralized agency to evaluate evidence and make decisions about price and access

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Value Assessment Framework: What is “Value”?

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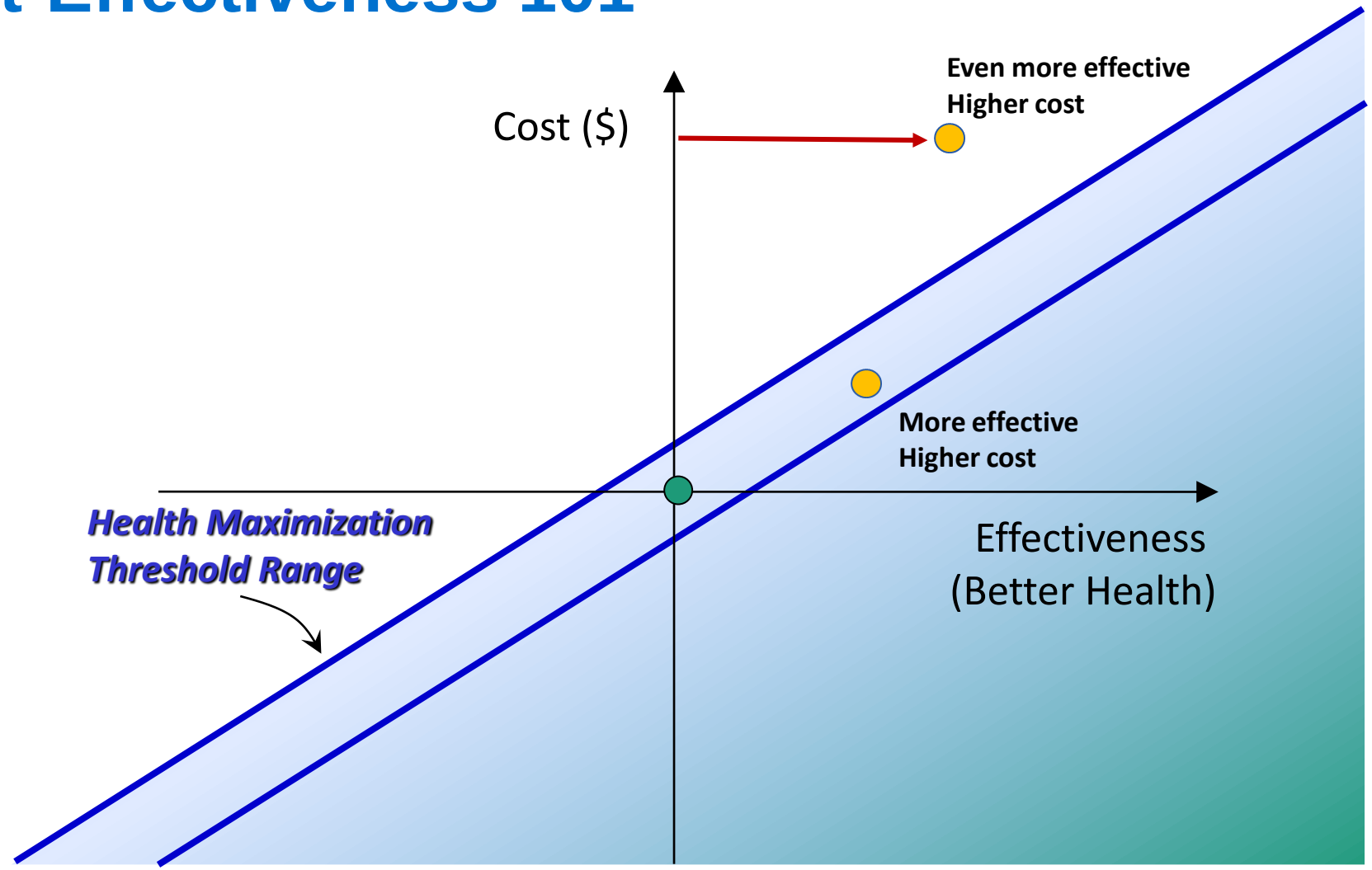
Cost-Effectiveness 101



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ICER's Value-based Price Benchmarks

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ICER's Value-based Price Benchmarks (Examples)

Assessment	Drugs	Discount Needed*
Spinal Muscular Atrophy	Spinraza	83-90%
Opioid Use Disorder	Probuphine and Vivitrol	53-69%
Rheumatoid Arthritis	Rinvoq	25-26%
Asthma	Xolair, Nucala, Cinqair, Fasenra, Dupixent	62-80%
Treatment-Resistant Depression	Spravato	25-52%

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Aduhelm: Famous for all the wrong reasons

PHARMA

Biogen's aducanumab crosses FDA finish line just in time to save its business

By **Noah Higgins-Dunn** • Jun 7, 2021 11:03am

December 21, 2021 10:15 AM EST *Updated 10:37 AM* | Pharma, FDA+

Alzheimer's experts call on FDA to pull Biogen's Aduhelm

Zachary Brennan
Senior Editor

Alzheimer's disease researchers along with medical professors from Harvard and Johns Hopkins issued a formal statement Monday asking the FDA to quickly pull Biogen's Aduhelm from the market.

December 20, 2021 07:33 AM EST *Updated 05:49 PM* | Pharma

Biogen slashes Aduhelm price in half, foreshadows significant layoffs as sales continue to stagnate

Jason Mast
Editor

In a surprise move, Biogen announced Monday that it will cut the price of its controversial Alzheimer's drug Aduhelm in half, slashing the cost from $56,000 to $28,000.

Why are we talking about aducanumab?

- Unprecedented approval from the FDA:
  - Ignored nearly unanimous vote from Advisory Committee against approval
  - Applied the Accelerated Approval Pathway retroactively
  - Allowed use of amyloid clearance as a surrogate endpoint after publicly saying it would not do so
- Investigative journalism exposed possibly improper coordination between FDA and Biogen
- Patients and their families left to fend for themselves

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https://www.statnews.com/2021/06/29/biogen-fda-alzheimers-drug-approval-aduhelm-project-onyx/

Aducanumab

- Monoclonal antibody targeting aggregated oligomers of beta-amyloid
- Studied in two phase 3 trials (“ENGAGE” and “EMERGE”) that were halted for futility and then re-analyzed as more data accumulated
- Broadly approved by the FDA in June 2021 under accelerated approval
- Label narrowed in July 2021 to say that it “should be initiated” in early disease (mild cognitive impairment [MCI] and mild AD)
- ICER’s public meeting, after extensive 8-month review, was July 15, 2021

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ENGAGE and EMERGE: Contemporaneous, Identical RCTs

Study	Group	N	F/U Months	Age, Years	Baseline CDR-SB, mean (SD)
ENGAGE (Study 301)	MCI due to AD or mild AD	Total: 1,647 70% ApoE+ 80% MCI	Planned 18 months*	70.1	2.41 (1.0)
EMERGE (Study 302)		Total: 1,638 67% ApoE+ 82% MCI		70.7	2.48 (1.0)

*Pre-specified futility analysis with data collected until December 2018.

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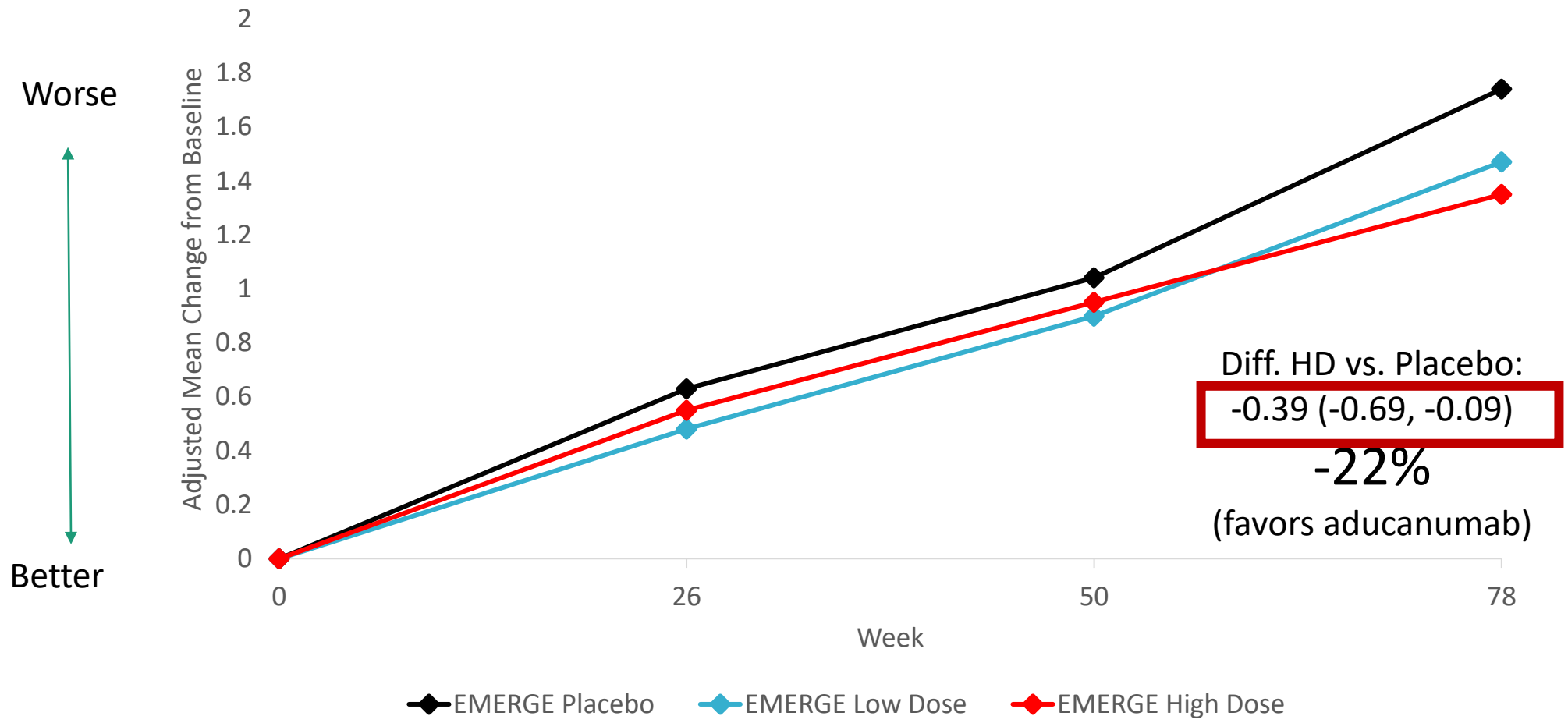
EMERGE Results: CDR-SB (ITT)



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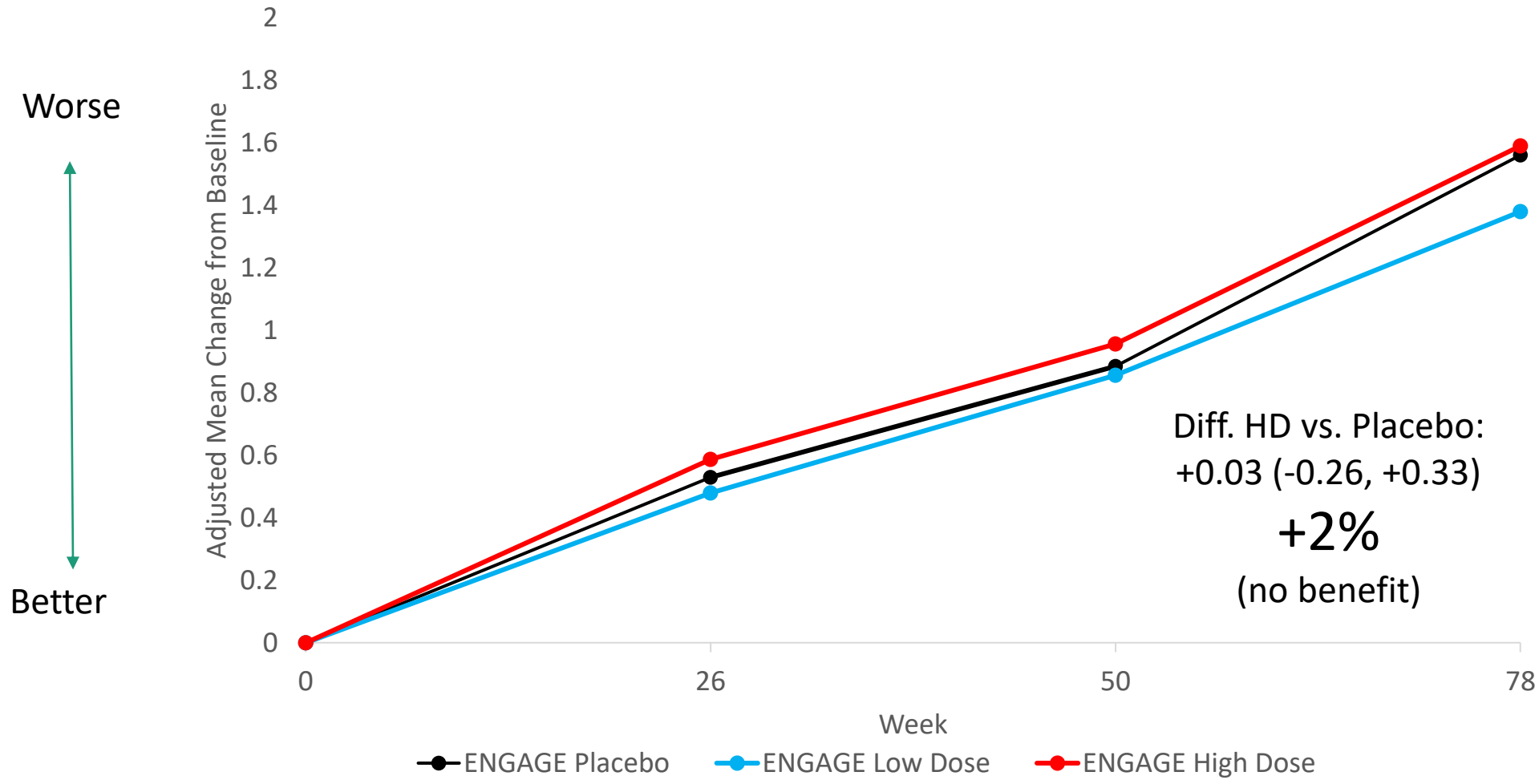
CDR-SB (ITT) - Clinical Dementia Rating Scale–Sum of Boxes, Intent to Treat

ENGAGE Results: CDR-SB (ITT)



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CDR-SB (ITT) - Clinical Dementia Rating Scale–Sum of Boxes, Intent to Treat

Manufacturer and FDA looked to reconcile trial results

- Appear to have started from premise that positive trial (EMERGE) was correct
- Post-hoc subgroup analyses performed
- Ended up focusing on fewer patients in ENGAGE having received full dose (10 mg/kg) because of different timing of protocol change that allowed higher dosing
  - EMERGE started one month after ENGAGE
  - 29% of patients in EMERGE and 22% of patients in ENGAGE received all fourteen doses of 10 mg/kg

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Controversies and Uncertainties

- Ultimately unclear why trials came to different conclusions
  - Post-hoc explanation related to dosing seems unlikely
- “Amyloid hypothesis” may be wrong or incomplete*
- Clinical significance of even EMERGE findings very uncertain
- Brain bleeding and swelling in the real world could be worse due to less careful monitoring
- Lack of diversity in studied population

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*will lecanamab results help answer this question?

Evidence Rating

- Aducanumab for treatment of patients with mild cognitive impairment or mild dementia due to Alzheimer's Disease:
  - **Insufficient ("I")**

I: Insufficient – Any situation in which the level of certainty in the evidence is low

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Economic Analysis

- Little information available on effectiveness beyond transition from MCI to mild AD
  - Assumed no benefit in slowing decline from moderate to severe disease based on expert opinion and prior trials of monoclonal antibodies
  - Assumed the benefit for slowing transition from mild AD to moderate AD was half that seen for MCI-mild AD

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Results: Incremental Cost-Effectiveness Ratios

	Cost per QALY Gained	Cost per evLYG	Cost per Additional Year in the Community
Health Care System Perspective	$1,330,000	$1,020,000	$1,270,000

Despite uncertainty in evidence, followed standard approach of seeking best estimate by pooling results from EMERGE and ENGAGE

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Value-Based Price Benchmarks and Potential Budget Impact

- If we assume the pooling of EMERGE and ENGAGE is best estimate of overall safety and effectiveness:
  - Value-Based Price Benchmark: **$3,000 to $8,400**
- Potential budget impact….

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Clinical and Cost-effectiveness: Bottom Lines

- Insufficient evidence to demonstrate that aducanumab provides a net health benefit
  - Best explanation for conflicting trials may be random play of chance
  - No particular reason to think the positive trial is more likely to be correct
- Known harms with brain bleeding and swelling, long-term effects unknown
- Given standard combination of results of the two trials, a reasonable price would be significantly less than the current list price

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Key Policy Recommendations

- Fair pricing is required to fulfill the social responsibility held by manufacturers to avoid financial toxicity that falls hardest on the most vulnerable patients
- Manufacturer must work with communities of color to ensure diverse populations are represented in clinical trials, and speed up its confirmatory trial
- Health plans and CMS may choose not to cover because there is insufficient evidence of benefit and known harms
- Regulators should use clinical endpoints reasonably likely to benefit patients

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Fall-out from approval

- Three members of the FDA Advisory Committee resigned
- Several major health systems refused to prescribe it
- CMS National Coverage Determination = will only reimburse if patients enrolled in clinical trial
- Biogen slashed price from $56,000 to $28,000

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https://www.statnews.com/2021/09/22/biogens-aduhelm-sales-slower-than-disclosed-forcing-company-to-consider-cost-cutting-measures/; https://endpts.com/new-aria-cases-dog-biogens-aduhelm-launch-in-another-blow-to-blockbuster-hopes-analyst/

Hemophilia Gene Therapy: The test case at our doorstep

Hemophilia A

- Increased tendency to bleed due to inherited deficiencies of factor VIII; Risk for life-threatening bleeds, but bleeds into joints or muscle more common and lead to pain and disability
- Patients with severe hemophilia and some with moderate hemophilia should use prophylaxis to prevent bleeding; Factor VIII prophylaxis multiple IV infusions per week or emicizumab subcutaneous injection every few weeks
- Investigational gene therapy - Valoctocogene roxaparvovec (Valrox)
  - AAV5 gene therapy for hemophilia A
  - One time infusion

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Hemophilia A: Overview of Evidence

Valrox & Emicizumab Key Trials

Trial	N	Key Outcome	Longest Follow-Up
GENEr8-1 Valrox Phase III	134	Factor VIII Activity Factor VIII Usage Annualized Bleeding Rate	2 years
BMN 270-201 Valrox Phase 2b	7	Treatment-Related AEs Factor VIII Usage Annualized Bleeding Rate	6 years
HAVEN 3 Emicizumab Phase III	48	Annualized Bleeding Rate Safety	2 years

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Valrox vs. FVIII Prophylaxis for Hemophilia A:
Key Study Results

- **Annualized bleeding rates decreased significantly up to 24 months**
  - All bleeds*: NR*
  - Treated bleeds: 85% reduction
  - Treated joint bleeds: 84% reduction

- **Reduced need for factor VIII prophylaxis**
  - 98% reduction in volume and number of infusions

- **Declining factor VIII activity over time**

Month 12		Month 24
42 IU/dL	→	24 IU/dL

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FVIII decline among 7 patients followed for five years

- 64 → 36.4 → 32.7 → 24.2 → 11.6

- Mild disease at 40%
- Moderate disease at 5%
- Severe disease at 1%

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Valrox vs. Emicizumab

- No direct comparison
- All bleeds and treated bleeds appear to have been reduced more with Valrox

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Summary and ICER Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Hemophilia A who require Factor VIII prophylaxis		
Valoctocogene Roxaparvovec	Factor prophylaxis	C++
Valoctocogene Roxaparvovec	Emicizumab	I

- **B+: Comparable of Incremental** – moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit
- **C++: Comparable or Better** – Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
- **I: Insufficient** – Any situation in which the level of certainty in the evidence is low

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Cost Effectiveness Section: Base Case Results

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Valoctocogene Roxaparvovec	$13,394,000*	$13,834,000	152	17.62	27.13	17.62
Emicizumab	$17,492,000	$18,004,000	153	17.49	27.13	17.49

*Valrox was projected to be a dominant treatment with lower costs, slightly lower bleeds, and higher QALYs at a placeholder price of $2.5m.

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QALY: quality-adjusted life year
evLY: equal value of life year

Value-based Price Benchmarks - Draft

	$50,000 per QALY gained	$100,000 per QALY gained	$150,000 per QALY gained	$200,000 per QALY gained
Valrox Base Case	$6,776,000	$6,782,000	$6,789,000	$6,796,000
$150,000 Cap Scenario				
Shared Savings (50:50)				
No Savings				

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QALY: quality-adjusted life year

Possible solutions

Where do we go from here?

- **Reimbursement with evidence development** – pay a lower price until clinical benefit proven
- **Value-based pricing** – clinical excellence commands a high-price, diminished incentive for me-too drugs; important consideration to how much social surplus accrues to the mnfr
- **Outcomes-based contracts (with guardrails)** – protects against treatment failures, waning clinical efficacy
- **National drug benefit** –reimbursement for all cell and gene therapies, central government agency negotiates price
- **Pooling/Re-insurance (Embarc model)** – purchasers pay a PMPM for unlimited access to gene and cell therapies

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