New Drug Update

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Disclosure

I have no financial interests or relationships to disclose.

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Pneumococcal Vaccine for Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023

TABLE 2. Pneumococcal vaccine schedules for adults aged ≥65 years, by underlying conditions — Advisory Committee on Immunization Practices, United States, 2023

Vaccine received previously at any age	Any or no underlying condition Schedule option A (PCV20 available)	No specified immunocompromising condition,* CSF leak, or cochlear implant Schedule option B (PCV15 and PPSV23 available)	Specified immunocompromising condition,* CSF leak, or cochlear implant Schedule option B (PCV15 and PPSV23 available)
None/unknown† or PCV7 only§	Administer a single dose of PCV20	Administer a single dose of PCV15, then after a ≥1 year interval since the PCV15 dose, administer a single dose of PPSV23	Administer a single dose of PCV15, then after ≥8 weeks since the PCV15 dose, administer a single dose of PPSV23
PPSV23 only§	Administer a single dose of PCV20 after a ≥1 year interval since the last PPSV23 dose	Administer a single dose of PCV15 after a ≥1 year interval since the last PPSV23 dose	Administer a single dose of PCV15 after a ≥1 year interval since the last PPSV23 dose
PCV13 only	Administer a single dose of PCV20 after a ≥1 year interval since the last PCV13 dose¶	Administer a single dose of PPSV23 after a ≥1 year interval since the last PCV13 dose**	Administer a single dose of PPSV23 after ≥8 weeks since the last PCV13 dose**
Both PCV13 and PPSV23 (any order of receipt) but has not yet received a dose of PPSV23 at age ≥65 years	Administer a single dose of PCV20 after a ≥5 year interval since the last PCV13 or PPSV23 dose¶	Administer a single dose of PPSV23 after a ≥1 year interval since the last PCV13 dose and a ≥5 year interval since the last PPSV23 dose**	Administer a single dose of PPSV23 after ≥8 weeks since the last PCV13 dose and ≥5 years since the last PPSV23 dose**
Both PCV13 and PPSV23 (any order), and the PPSV23 was administered at age ≥65 years	Together, with the patient, vaccine providers may choose to administer a single dose of PCV20 to adults aged ≥65 years who already have received PCV13 (but not PCV15 or PCV20) at any age and PPSV23 at age ≥65 years. The interval should be ≥5 years since the last PCV13 or PPSV23 dose.¶,††	N/A	N/A

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Pneumococcal Vaccine for Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023

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TABLE 3. Pneumococcal vaccine schedules for adults aged 19–64 years with specified immunocompromising conditions* — Advisory Committee on Immunization Practices, United States, 2023

Vaccine received previously at any age	Schedule option A (PCV20 available)	Schedule option B (PCV15 and PPSV23 available)
None/unknown† or PCV7 only§ at any age	Administer a single dose of PCV20	Administer a single dose of PCV15, then after a ≥8 week interval since the PCV15 dose, administer a single dose of PPSV23
PPSV23 only§	Administer a single dose of PCV20 after a ≥1 year interval since the last PPSV23 dose	Administer a single dose of PCV15 after a ≥1 year interval since the last PPSV23 dose
PCV13 only	Administer a single dose of PCV20 after a ≥1 year interval since the last PCV13 dose¶	Administer a single dose of PPSV23 after a ≥8 week interval since the last PCV13 dose. Administer a second PPSV23 dose after a ≥5 year interval since the last PPSV23 dose. Review the pneumococcal vaccine recommendations again when the patient turns age 65 years.**
PCV13 and 1 dose of PPSV23 (any order of receipt)	Administer a single dose of PCV20 after a ≥5 year interval since the last PCV13 or PPSV23 dose¶	Administer a single dose of PPSV23 after a ≥8 week interval since the last PCV13 dose and a ≥5 year interval since the last PPSV23 dose. Review the pneumococcal vaccine recommendations again when the patient turns age 65 years.**
PCV13 and 2 doses of PPSV23 (any order of receipt)	Administer a single dose of PCV20 after a ≥5 year interval since the last PCV13 or PPSV23 dose¶	Review the pneumococcal vaccine recommendations again when the patient turns age 65 years**

Abbreviations: ACIP = Advisory Committee on Immunization Practices; CSF = cerebrospinal fluid; PCV7 = 7-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

* Chronic renal failure congenital or acquired asplenia, congenital or acquired immunodeficiency (including B-[humoral] or T-lymphocyte deficiency, complement deficiencies [particularly C1, C2, C3, and C4 deficiencies], and phagocytic disorders [excluding chronic granulomatous disease]), generalized malignancy, HIV infection, Hodgkin disease, iatrogenic immunosuppression (including disease requiring treatment with immunosuppressive drugs such as long-term systemic corticosteroids and radiation therapy), leukemia, lymphoma, multiple myeloma, nephrotic syndrome, sickle cell disease and other hemoglobinopathies, and solid

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Pneumococcal Vaccine for Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023

TABLE 5. Pneumococcal vaccine schedules for adults aged 19–64 years with a chronic medical condition† — Advisory Committee on Immunization Practices, United States, 2023

Vaccine received previously	Schedule option A (PCV20 available)	Schedule option B (PCV15 and PPSV23 available)
None† or PCV7 only§ at any age	Administer a single dose of PCV20	Administer a single dose of PCV15, then after a ≥1 year interval since the last dose, administer a single dose of PPSV23
PPSV23 only§	Administer a single dose of PCV20 after a ≥1 year interval since the last PPSV23 dose	Administer a single dose of PCV15 after a ≥1 year interval since the last PPSV23 dose
PCV13 only§,¶	After a ≥1 year interval since the last dose, administer a single dose of PCV20	Administer a single dose of PPSV23 after a ≥1 year interval since the last PCV13 dose. Review the pneumococcal vaccine recommendations again when the patient turns age 65 years.
PCV13 and PPSV23§,¶	No vaccines are recommended at this time. Review the pneumococcal vaccine recommendations again when the patient turns age 65 years.	

Abbreviations: ACIP = Advisory Committee on Immunization Practices; PCV7 = 7-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

* Alcoholism; chronic heart disease, including congestive heart failure and cardiomyopathies; chronic liver disease; chronic lung disease, including chronic obstructive pulmonary disease, emphysema, and asthma; cigarette smoking; or diabetes mellitus.

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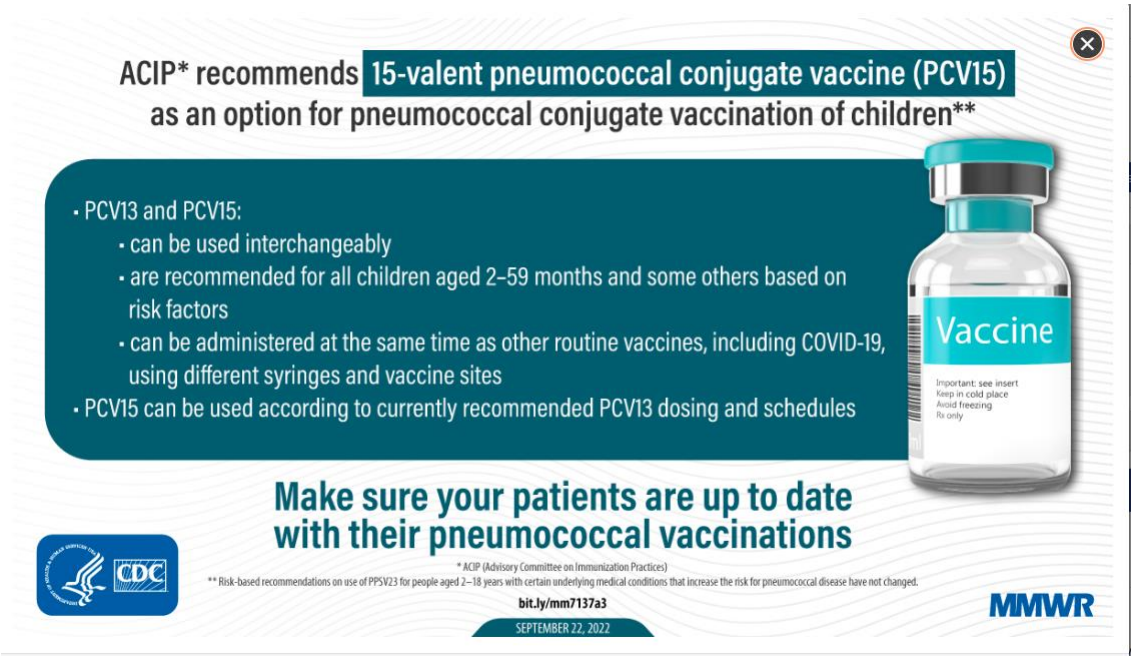

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PCV-20 – Prevnar 20 Update

- **April 27, 2023, The FDA has approved Pfizer's 20-valent Pneumococcal Conjugate Vaccine (Prevnar 20) to prevent invasive pneumococcal disease (IPD) caused by 20 Streptococcus pneumoniae serotypes among infants and children 6 weeks through 17 years of age, as well as for the prevention of otitis media in infants 6 weeks through 5 years of age caused by the original 7 serotypes contained in the vaccine.**
- **Dose - a 4-dose immunization series at 2, 4, 6, and 12 through 15 months of age, first dose may be given at 6 weeks of age.**
- **6-22-2023 The ACIP also unanimously recommended PCV-20 for children.**
- **CDC recommends routine administration of pneumococcal conjugate vaccine (PCV15 or PCV20) for all children younger than 5 years of age: Give PCV15 or PCV20 to infants as a series of 4 doses. No preference as data is limited currently.**

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21-valent Pneumococcal Conjugate Vaccine (PCV-21) – Capvaxive by Merck

- **6-17-2024 the FDA approved pneumococcal 21-valent conjugate vaccine (PCV-21 vaccine) (Capvaxive) following priority review, and accelerated review, for the prevention of invasive pneumococcal disease (IPD) and pneumococcal pneumonia in adults ages 18 years and older.**
- This is the **first pneumococcal vaccine that is specifically designed to protect against the serotypes that primarily infect older adults.** Data has shown that **the serotypes included in this vaccine are responsible for approximately 84% of IPD in adults aged 50 years and older.** The vaccine covers 21 serotypes, **including eight that are not targeted by any other available pneumococcal vaccines**, specifically serotypes 15A, 15C, 16F, 23A, 23B, 24F, 31, and 35B.

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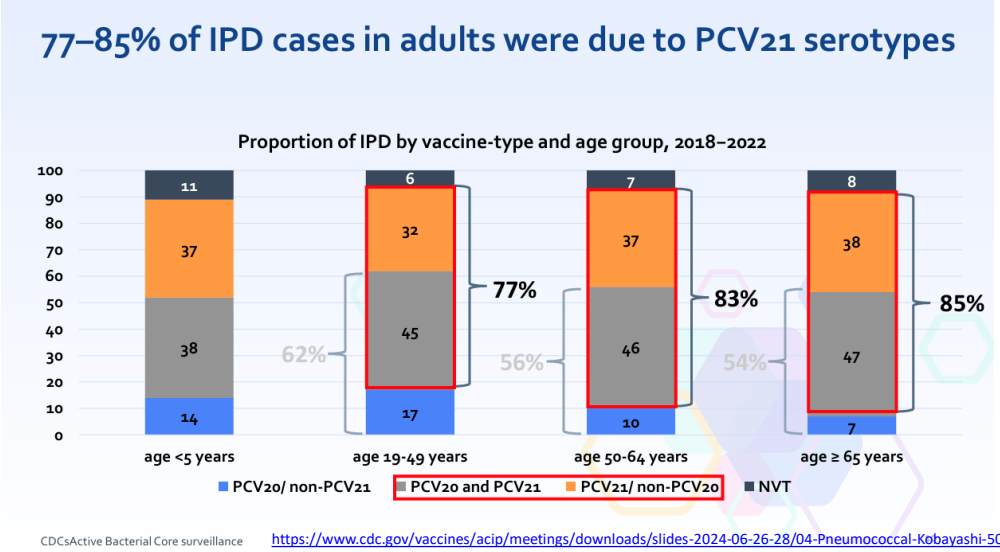
ACIP Working Group on PCV-21 in Adults



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21-valent Pneumococcal Conjugate Vaccine (PCV-21) – Capvaxive

- **The indication for the prevention of pneumonia caused by S. pneumoniae serotypes** 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B **is approved under accelerated approval based on immune responses as measured by opsonophagocytic activity (OPA).**
- The **accelerated approval requires, among other things, that you conduct adequate and well-controlled studies to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as prevention of pneumococcal pneumonia caused by the serotypes in Capvaxive.** Study completion due 6/29/2029.

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21-valent Pneumococcal Conjugate Vaccine (PCV-21) – Capvaxive

- **June 27, 2024, the ACIP voted unanimously to recommend PCV-21 as an option for adults 65 years of age and older for pneumococcal vaccination for:**
  - **Adults 65 years of age and older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown;**
  - **Adults 19-64 years of age with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown;**
  - **Adults 19 years of age and older who have started their pneumococcal vaccine series with PCV13 (pneumococcal 13-valent conjugate vaccine) but have not received all recommended PPSV23 (pneumococcal 23-valent polysaccharide vaccine) doses.**
  - **Additionally, shared clinical decision-making is recommended regarding use of a supplemental dose of Capvaxive for adults 65 years of age and older who have completed their vaccine series with both PCV13 and PPSV23.**

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ACIP Meeting 6-27-2024

Updated 2024-2025 Flu Vaccine Recommendation

Updated 2024-2025 flu vaccines will all be trivalent and will protect against an H1N1, H3N2 and a B/Victoria lineage virus. The composition of this season's vaccine compared to last has been updated with a new influenza A(H3N2) virus.

- **CDC recommends everyone 6 months of age and older, with rare exceptions, receive an updated 2024-2025 flu vaccine to reduce the risk of influenza and** its potentially serious complications this fall and winter.
- Most people need only one dose of the flu vaccine each season. While CDC recommends flu vaccination as long as influenza viruses are circulating, **September and October remain the best times for most people to get vaccinated**. **Flu vaccination in July and August is not recommended for most people.**

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ACIP Meeting 6/27/2024

- The **committee voted 15-0 to recommend that people aged 65 years or older receive a high-dose inactivated influenza vaccine, adjuvanted inactivated influenza vaccine, or recombinant influenza vaccine over any of the standard-dose unadjuvanted, inactivated vaccines.**
  - **ACIP Mtg 6/22-23.2022**
- **For the 2024-2025 flu season, there are three flu vaccines that are preferentially recommended for people 65 years and older. These are Fluzone High-Dose Trivalent vaccine (contains four times the amount of antigen), Flublok Trivalent recombinant flu vaccine (contains three times the amount of antigen) and Fluad Trivalent adjuvanted flu vaccine.**

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ACIP Meeting 6/27/2024

- **ACIP passed a unanimous motion (11-0) recommending that high-dose (HD-IIV3) and adjuvanted (aIIV3) inactivated influenza vaccines are acceptable options for influenza vaccination of solid organ transplant recipients who are 18-64 years old and who are taking immunosuppressive medication regimens**, without a preference over other age appropriate inactivated or recombinant influenza vaccines.

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Measles

- April 4.2024 - **Measles cases in the U.S. are climbing, as of May 30, 2024, a total of 146 measles cases were reported by 21 states, while in 2023, 58 cases were reported over the entire year.**
- The **reason is not enough kids are getting vaccinated. For herd immunity, about 95% or more of a population needs to be vaccinated,** but most countries around the world have been below that threshold for years. **By 2019, 86% of kids worldwide had been vaccinated with a dose by their second birthday, but that number dropped even further to 81% in 2021.**
  - https://www.msn.com/en-us/health/other/why-measles-cases-are-rising-right-now/ar-BB1j3L20
  - https://www.cdc.gov/measles/cases-outbreaks.html
- **The ACIP committee gave the green light to a second MMR vaccine, Priorix (GSK), for use as an option in the U.S. in people aged 6 months or older. Previously, only Merck's MMR vaccine was available.** (ACIP Meeting 6/22-23/2022)

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Measles

Age:

Under 5 years: 65 (45%)

5-19 years: 33 (23%)

20+ years: 48 (33%)

Vaccination Status:

Unvaccinated or Unknown: 83%

One MMR dose: 12%

Two MMR doses: 5%

U.S. Hospitalizations in 2024:

55% of cases hospitalized (80 of 146) for isolation or for management of measles complications.

Percent of Age Group Hospitalized

Under 5 years: 65% (42 of 65)

5-19 years: 42% (14 of 33)

20+ years: 50% (24 of 48)

https://www.cdc.gov/measles/data-research/index.html
updated May 31, 2024

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Measles

- **One dose of MMR vaccine is approximately 93% effective at preventing measles; two doses are approximately 97% effective. Almost everyone who does not respond to the measles component of the first dose of MMR vaccine at age 12 months or older will respond to the second dose. Therefore, the second dose of MMR is administered to address primary vaccine failure.**
- **CDC recommends routine childhood immunization for MMR vaccine starting with the first dose at 12 through 15 months of age, and the second dose at 4 through 6 years of age or at least 28 days following the first dose.** The **measles-mumps-rubella-varicella (MMRV) vaccine is also available to children 12 months through 12 years of age (not for patients >12 y/o); the minimum interval between doses is three months.**
  - https://www.cdc.gov/measles/hcp/index.html

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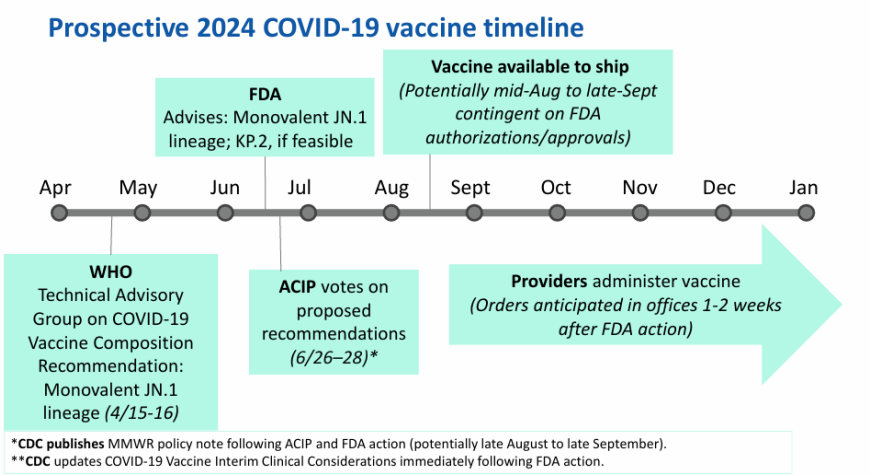
FDA Recommendations for COVID-19 Vaccines for Fall 2024

- **June 5, 2024 FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) met on June 5, 2024, to discuss and make recommendations on the selection of the 2024-2025 Formula for COVID-19 vaccines** for use in the United States beginning in the fall of 2024.
- **Current vaccines (2023-2024) built to fight XBB.1.5 also don't provide as much protection against JN.1 and several sub-variants driving cases The committee unanimously voted to recommend a monovalent JN.1-lineage vaccine composition. Based on the totality of the evidence, FDA has advised the manufacturers of the licensed and authorized COVID-19 vaccines that the COVID-19 vaccines for use in the United States beginning in fall 2024 should be monovalent JN.1 vaccines to more closely match currently circulating SARS-CoV-2 viruses.**
  - https://www.fda.gov/vaccines-blood-biologics/updated-covid-19-vaccines-use-united-states-beginning-fall-2024#:~:text=FDA%27s%20Vaccines%20and%20Related%20Biological,to%20recommend%20a%20monovalent%20JN.

19

ACIP Meeting 6/27/2024

ACIP unanimously recommends 2024-2025 COVID-19 JN1 monovalent vaccines as authorized or approved by FDA in persons ≥6 months of age.



https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-06-26-28/07-COVID-Stokely-508.pdf

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% of Patients Up-to-date with COVID 19 Vaccines

- As of May 11, 2024, vaccination coverage among children (6 mo-17 y/o) was 14.4%.
  - By age group: Vaccination coverage increased with increasing age, 6 mo to 4 y/o (6%), 5-11 y/o (13.3%) and 12-17 y/o (17.9%).
  - By race and ethnicity: Vaccination coverage was highest among white, non-Hispanic children (15.2%) and lowest among Black, non-Hispanic children (10.9%)
- As of May 11, 2024, vaccination coverage among adults (age 18 and above) was 22.5%.
  - Data source, National Immunization Survey—COVID Child Module (NIS-CCM) and National Immunization Survey—Flu (NIS-Flu): https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/children-coverage-vaccination.html
- As of Feb. 1, 2024, overall, VE was 58% (95% CI = 48%–65%) among those who received testing 7–59 days after receipt of updated vaccine and 49% (95% CI = 36%–58%) among those who received testing 60–119 days after receipt of updated vaccine. https://www.cdc.gov/mmwr/volumes/73/wr/mm7304a2.htm

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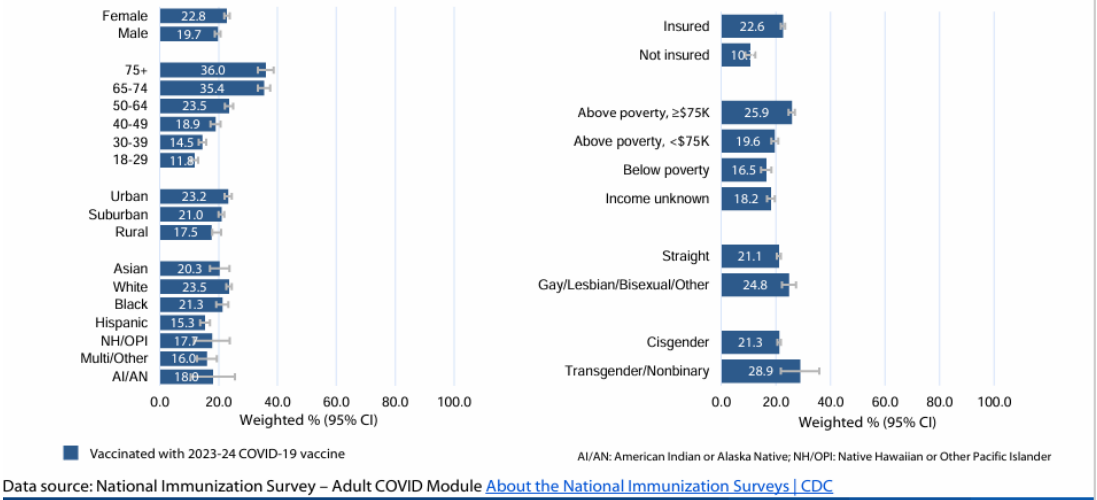
COVID-19 Vaccination Status Among Adults Age ≥18 Years by Demographics, NIS-ACM, April 28-May 25, 2024 (n=47,953)



Data source: National Immunization Survey – Adult COVID Module About the National Immunization Surveys | CDC

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Missed COVID-19 Vaccine Doses

- Missed Vaccine Doses Tied to Worse COVID-19 Outcomes **People in the UK who did not receive all the doses of the vaccine for which they were eligible had up to 4 times the risk of being hospitalized or dying from COVID-19 compared with those who were fully vaccinated,** according to electronic health record data taken from the entire population aged 5 years or older. **Rates of under vaccination ranged from about 33% to almost 50% across the UK**, with the highest rates in Northern Ireland. The study in The Lancet looked at data from June to September 2022. The **researchers estimated that 7000 deaths and hospitalizations could have been avoided if UK citizens had been fully vaccinated at the start of the 4-month study period**. Published Online: January 31, 2024. doi:10.1001/jama.2023.28340

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Novavax COVID-19 Vaccine, Adjuvanted (2023–2024 Formula)

- On October 3, 2023, the **FDA issued emergency use authorization (EUA) of the updated Novavax COVID-19 Vaccine, Adjuvanted (2023–2024 Formula), for people age 12 and older.** The monovalent vaccine was updated to include the spike protein from the SARS-CoV-2 Omicron variant lineage XBB.1.5.
  - At the time of authorization, the Novavax product was automatically **included among options recommended for use by CDC under the terms of the September 12 Advisory Committee on Immunization Practices (ACIP) vote for a broad recommendation for all 2023–2024 updated monovalent, XBB-containing COVID-19 vaccines as authorized or approved by FDA**. Insurance coverage under Medicaid, Medicare, and all Affordable Care Act-compliant insurance plans is triggered by the FDA authorization.
  - https://www.fda.gov/news-events/press-announcements/fda-authorizes-updated-novavax-covid-19-vaccine-formulated-better-protect-against-currently

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Respiratory Syncytial Virus

- **RSV is the most frequent cause of lower respiratory tract illness in infants worldwide. In most parts of the U.S., RSV circulation is seasonal, typically starting during the fall and peaking in the winter.** The virus is especially common in children, and **most individuals can be expected to be infected with RSV by the time they reach two years of age.**
- RSV most often causes cold-like symptoms in infants and young children, it can also lead to serious LRTD such as pneumonia and bronchiolitis (swelling of the small airway passages in the lungs). In infants and children, the risk of RSV-associated LRTD is highest during the first year of life. **According to the Centers for Disease Control and Prevention, RSV is the leading cause of infant hospitalization in the U.S.**
  - https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants

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Respiratory Syncytial Virus Vaccine, Adjuvanted – Arexvy

- **May 3, 2023** - GSK announced that the US Food and Drug Administration (FDA) has **approved Arexvy (respiratory syncytial virus vaccine, adjuvanted) for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older. This is the first RSV vaccine for older adults to be approved anywhere in the world.**
- While GSK's vaccine has shown **efficacy of 82.6% in preventing RSV in year one and 94.1% efficacy in preventing severe disease**, those **figures drop to 77.3% and 84.6% in the second RSV season, respectively, with a median follow-up time of 14 months from administration.**
  - https://www.fiercepharma.com/pharma/cdc-advisory-panel-examines-gsk-pfizer-rsv-data-will-vote-afternoon-recommended-use

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Respiratory Syncytial Virus Unadjuvanted Bivalent Stabilized Prefusion F Protein Vaccine – Abrysvo by Pfizer

- **May 31, 2023, the FDA approved Pfizer's Respiratory Syncytial Virus unadjuvanted bivalent A and B strain stabilized prefusion F protein vaccine for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years and older.**
- **Pfizer's vaccine has shown 66.7% efficacy in the first year against RSV, with 85.7% protection against severe disease. In the second season, at month 18, the efficacy numbers wane to 49% and 78.6%, respectively.**
  - Both companies plan to test a subset of trial participants with a booster dose after two years post initial administration.
- The CDC also provided a cost-effectiveness model for the two vaccines, which showed GSK's vaccine providing significantly more value—even when priced at $270 per dose compared to $200 for the Pfizer vaccine.
  - **https://www.fiercepharma.com/pharma/cdc-advisory-panel-examines-gsk-pfizer-rsv-data-will-vote-afternoon-recommended-use**

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CDC Endorses ACIP Recommendations for RSV Vaccines

- **6/29/2023 CDC Director Rochelle P. Walensky, M.D., M.P.H., endorsed the CDC Advisory Committee on Immunization Practices' (ACIP) recommendations for use of new Respiratory Syncytial Virus (RSV) vaccines from GSK and Pfizer for people ages 60 years and older, using shared clinical decision-making.** This means these individuals may receive a single dose of the vaccine based on discussions with their healthcare provider about whether RSV vaccination is right for them.
- **Covered by Medicare Part D and will be primarily offered in pharmacies.**
  - https://www.cdc.gov/media/releases/2023/s0629-rsv.html

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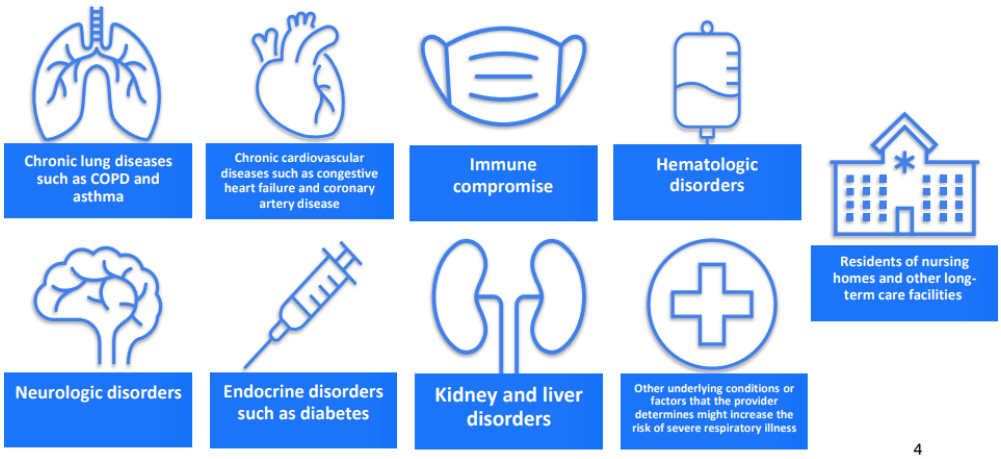
ACIP Meeting 6-21-2023

If shared clinical decision-making is recommended adults who may be at higher risk of RSV disease include persons with:



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https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-06-21-23/07-RSV-Adults-Britton-508.pdf

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mRNA-based RSV Vaccine, Encoding the Stabilized RSV Prefusion F Glycoprotein- mRESVIA by Moderna

- **May 31, 2024, FDA approved MRESVIA is indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older.**
- Each 0.5 mL dose of MRESVIA contains 50 mcg of nucleoside modified mRNA encoding the RSV F glycoprotein.
- Data is from the **on-going Phase 2-3, 35,541 patient Conquer RSV Study.**
  - N Engl J Med 2023;389:2233-44.

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mRNA-based RSV Vaccine, Encoding the Stabilized RSV Prefusion F Glycoprotein- mRESVIA

- The **two primary efficacy end points were the prevention of RSV-associated lower respiratory tract disease with at least two signs or symptoms and with at least three signs or symptoms.** A key secondary efficacy end point was the prevention of RSV-associated acute respiratory disease. **Median follow-up was 112 days.**
- **Vaccine efficacy was 83.7%** (95.88% confidence interval [CI], 66.0 to 92.2) **against RSV-associated lower respiratory tract disease with at least two signs or symptoms and 82.4%** (96.36% CI, 34.8 to 95.3) **against the disease with at least three signs or symptoms. Vaccine efficacy was 68.4%** (95% CI, 50.9 to 79.7) **against RSV-associated acute respiratory disease.** Protection was observed against both RSV sub types (A and B) and was generally consistent across subgroups defined according to age and coexisting conditions.

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ACIP Meeting RSV Vaccine Update

- **Feb 29, 2024 - As to the benefits of RSV vaccination, Melgar and CDC colleagues projected that over the course of two RSV seasons, every 1 million doses administered in the older adult population would prevent an estimated 23,000-26,000 outpatient visits, 2,200-2,700 hospitalizations, 420-550 ICU admissions, and 120-140 in-hospital deaths.**
- However, uptake of the RSV vaccines has been low**. Only about 22% of adults ages 60 and older had received an RSV vaccine through February 2024**, according to the CDC.
- "Based on this review of currently available data, the [vaccination] work group continues to believe **that the estimated benefits of RSV vaccination outweigh potential risks when vaccination is implemented using the current recommendation."**
  - https://www.medpagetoday.com/infectiousdisease/vaccines/108969?xid=nl_mpt_DHE_20240229&eun=g326027d0r&utm_source=Sailthru&utm_medium=email&utm_campaign=Daily%20Headlines%20Evening%202024-02-29&utm_term=NL_Daily_DHE_dual-gmail-definition

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Respiratory Syncytial Virus Vaccine, Adjuvanted – Arexvy

- **June 7, 2024 - The FDA expanded the approval of GSK's respiratory syncytial virus (RSV) vaccine (Arexvy) to include adults ages 50 to 59 at risk of RSV-related lower respiratory tract disease (LRTD) due to underlying conditions.**
- The new approval was based on results of a double-blind phase III **multinational trial that demonstrated noninferior immune responses with the vaccine for 1,140 participants ages 50 to 59 (half of whom had high-risk conditions for RSV-LRTD) versus older adults**. In both of the younger groups, RSV-A and RSV-B neutralization titers were similar 1 month after administration of a single vaccine dose compared to the older group.
  - https://us.gsk.com/en-us/media/press-releases/us-fda-approves-expanded-age-indication-for-gsk-s-arexvy-the-first-respiratory-syncytial-virus-rsv-vaccine-for-adults-aged-50-59-at-increased-risk/

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ACIP Meeting 6-26-2024

- **All adults ages 75 years and older should receive a single dose of any respiratory syncytial virus (RSV) vaccine, and adults ages 60 to 74 years who are at increased risk of severe RSV disease should receive a vaccine, according to a unanimous 11-0 vote** by the CDC's Advisory Committee on Immunization Practices (ACIP).
- Also, **people who have already received the RSV vaccine are not recommended to receive a booster, based on data that showed another dose did not improve outcomes.**
- **These recommendations supplant the current recommendation that adults ages 60 and older may receive RSV vaccination after engaging in shared clinical decision-making with their healthcare provider.**

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ACIP Meeting 6-26-2024

- **The committee decided there was not enough data on benefits versus risks to recommend for or against the use of GSK's Arexvy vaccine in people ages 50 to 59 years at risk for severe RSV-associated disease,** according to Amadea Britton, MD, co-lead of the Adult RSV Vaccine Work Group. On June 10, the FDA expanded the approval opens in a new tab or window of Arexvy to include at-risk adults in this age group.
- **"This does not mean that the Work Group feels that RSV disease in this age group is unimportant," she said. "This opinion is also not a recommendation against the use of the RSV vaccine in adults aged 50 to 59 years. Rather, the Work Group believes more information is needed to make a population-level policy."**

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ACIP Meeting 6-26-2024

- **The benefits of the RSV vaccine in older adults continue to outweigh the small documented risk of Guillain-Barre syndrome, Michael Melgar, MD, co-lead of the Adult RSV Work Group**, said in a presentation. **"Bottom line, preventable outcomes far exceed potential cases of Guillain-Barre syndrome for both [GSK and Pfizer] vaccine products,"**

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Respiratory Syncytial Virus Unadjuvanted Bivalent Stabilized Prefusion F Protein Vaccine – Abrysvo

- **August 21,2023 The FDA approved Abrysvo (Respiratory Syncytial Virus Vaccine), the first vaccine approved for use in pregnant individuals to prevent lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age**. Abrysvo is **approved for use at 32 through 36 weeks gestational age of pregnancy.** Abrysvo is administered as a single dose injection into the muscle.
- The application was **granted Priority Review status and Fast Track and Breakthrough Therapy designations.**
  - https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants

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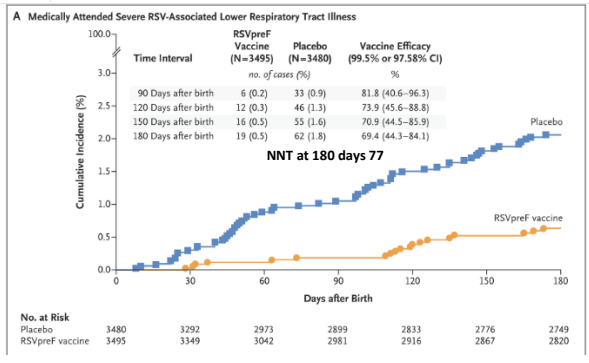
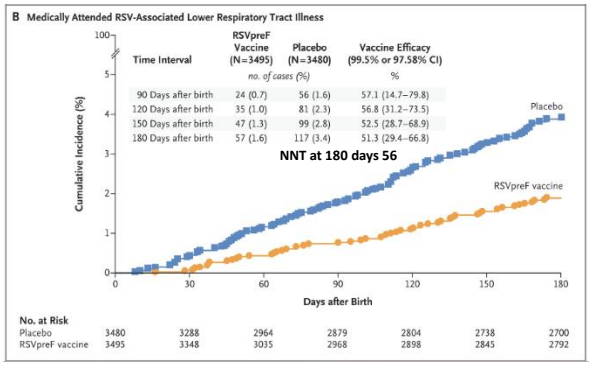
Bivalent Prefusion F Vaccine (Abrysvo) in Pregnancy to Prevent RSV Illness in Infants: MATISSE Study





N Engl J Med 2023; 388:1451-1464

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Respiratory Syncytial Virus Unadjuvanted Bivalent Stabilized Prefusion F Protein Vaccine – Abrysvo

- The Prescribing Information for Abrysvo includes a warning to inform that a **numerical imbalance in preterm births in Abrysvo recipients (5.7%) occurred compared to those who received placebo (4.7%).** The available data are insufficient to establish or exclude a causal relationship between preterm birth and Abrysvo. Specifically, the warning informs healthcare providers that to **avoid the potential risk of preterm birth with use of Abrysvo before 32 weeks of gestation, administer Abrysvo as indicated in pregnant individuals at 32 through 36 weeks gestational age.**
  - Pregnant individuals who were at increased risk of preterm birth were generally excluded from clinical studies of Abrysvo.
- The **FDA is requiring the company to conduct post-marketing studies to assess the signal of serious risk of preterm birth and to assess hypertensive disorders of pregnancy, including pre-eclampsia.**
  - https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants

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Nirsevimab-alip – Beyfortus by MedImmune/AstraZeneca and Sanofi

- **July 17, 2023, the U.S. Food and Drug Administration approved the monoclonal antibody Beyfortus (nirsevimab-alip) for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and in children up to 24 months of age who remain vulnerable to severe RSV disease** through their second RSV season.
  - One dose of Beyfortus, administered as a **single intramuscular injection prior to or during RSV season**, may provide protection during the RSV season.
  - **The terminal half-life is ~71 days and the expected duration of effect is ~5 months after a single dose.**

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Updated Recommendations Nirsevimab – Beyfortus
by ACIP and AAP 8-15-2023

August 15, 2023: ACIP and AAP Recommendations for the Use of the Monoclonal Antibody Nirsevimab for the Prevention of RSV Disease.

- **Nirsevimab is preferred and is recommended for:**
- **All infants younger than 8 months born during or entering their first RSV season, including those recommended by the American Academy of Pediatrics (AAP) to receive palivizumab;**
- **Infants and children aged 8 through 19 months who are at increased risk of severe RSV disease and entering their second RSV season, including those recommended by the AAP to receive palivizumab.**
  - **Per the FDA label, children who have received nirsevimab should not receive palivizumab for the same RSV season.**

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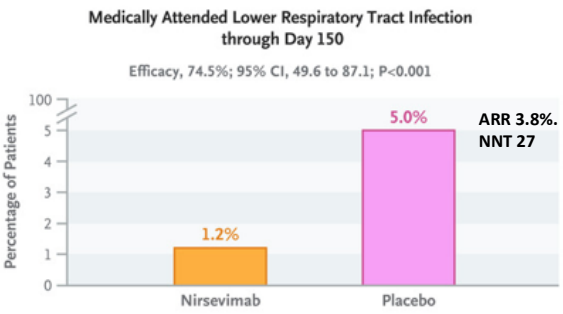
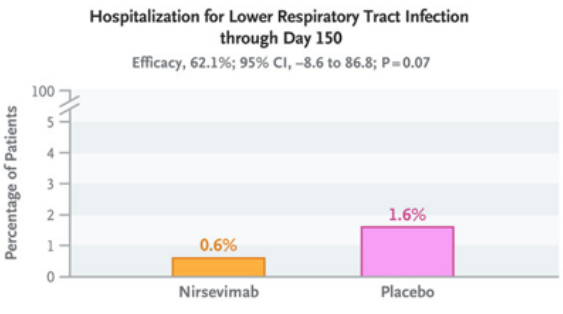
Nirsevimab-Beyfortus for Prevention of RSV in Healthy Late-Preterm and Term Infants - The MELODY Study

Randomly assigned, in a 2:1 ratio, **1490 infants who had been born at a gestational age of at least 35 weeks to receive a single intramuscular injection of nirsevimab or placebo before the start of an RSV season.** The **primary efficacy end point was medically attended RSV-associated lower respiratory tract infection through 150 days after the injection. The secondary efficacy end point was hospitalization for RSV-associated lower respiratory tract infection through 150 days after the injection.**

Adverse events primarily rash and injection site reactions were reported in 67 of 987 infants (6.8%) who received nirsevimab and in 36 of 491 infants (7.3%) who received placebo.

N Engl J Med 2022; 386:837-846





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Updated Recommendations Nirsevimab – Beyfortus

- **Equity in access to nirsevimab is of the highest priority to the AAP. While not technically a vaccine (it is a monoclonal antibody) it is covered by the Vaccines for Children (VFC) program. It is available through both the Vaccines for Children (VFC) program and directly from Sanofi.**
- **There is a CDC produced Vaccine Information Sheet (VIS-Like) for Nirsevimab and you do need to report administration to your states Immunization Information System (IIS).**
- **Early CDC surveillance data show that nirsevimab is 90% effective at preventing respiratory syncytial virus-associated hospitalization in infants.** Morbidity and Mortality Weekly Report (MMWR) (CDC) March 7, 2024

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Palivizumab - Synagis

- **The first FDA approved monoclonal antibody, palivizumab (Synagis), is limited to children under 24 months of age with certain conditions that place them at high risk for severe RSV disease**. It must be **given once a month during RSV season typically November - April.**
  - **Palivizumab is administered intramuscularly at a dosage of 15 mg/kg once a month.**
- **Therapeutic Efficacy? A recent 2019 Cochrane systematic review of 7 randomized controlled trials comparing the therapeutic use of RSV immunoglobulins, palivizumab, or motavizumab versus placebo in 486 hospitalized infants found no impact on mortality, length of hospital stay, or severity of illness. No effect on mortality was observed in another study of patients with hematologic diseases treated with palivizumab from 2007 to 2016.** (Leuk Lymphoma. 2019;60(1):85–91).

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Updated Recommendations Nirsevimab – Beyfortus
by ACIP and AAP 8-15-2023

Timing of nirsevimab

- Providers should **aim for nirsevimab administration in the first week of life for infants born shortly before and during the RSV season (Oct 1-March 31).**
- **Nirsevimab may be given to age-eligible infants and children (8-19 mo)who have not yet received a dose at any time during the season.**
- **Only children who meet high-risk criteria should receive more than one dose of nirsevimab** – one dose in their first RSV season and one dose in their second RSV season. **Healthy newborns born at the end of RSV season who received nirsevimab around the time of delivery (first RSV season) should not receive a second dose entering their second season even if they are <8 months of age**; conversely, **healthy infants born at the end of their first RSV season who did NOT receive nirsevimab and are <8 months of age entering their second RSV season may receive one dose of nirsevimab.**

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Updated Recommendations Nirsevimab – Beyfortus
by ACIP and AAP 8-15-2023

- Children 8 through 19 months of age who are **recommended to receive nirsevimab when entering their second RSV season because of increased risk of severe disease**
- **Children with chronic lung disease of prematurity** who required medical support (**chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season.**
- Children who are **severely immunocompromised.**
- Children with **cystic fibrosis who have manifestations of severe lung disease** (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest imaging that persist when stable) or have weight-for-length that is <10th percentile.
- **American Indian and Alaska Native children** (note that this is a **new** group for whom second-season prophylaxis is recommended in contrast to the current palivizumab recommendations).

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Respiratory Syncytial Virus (RSV) Vaccine Administration Errors in Young Children and Pregnant People

- **The Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) have received reports of the Pfizer (Abrsyvo) or GSK (Arexvy) RSV vaccines being administered in error to young children (25 reports in children <2 y/o). CDC and FDA have also received 128 reports of the GSK RSV vaccine (Arexvy) being administered in error to pregnant people.**
- **For infants and young children who are recommended to receive nirsevimab but received either the Pfizer (Abrysvo) or GSK (Arexvy) RSV vaccine in error, administer a dose of nirsevimab.**
- **For pregnant people who have received the GSK RSV vaccine (Arexvy) in error, do not give a dose of the Pfizer RSV vaccine (Abrysvo). Instead, the infant (if younger than 8 months) should receive nirsevimab during RSV season (October through March in most of the continental United States).**
  - COCA Now: CDC Clinician Outreach and Communication Activity January 22, 2024

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Global Initiative for Chronic Obstructive Lung Disease

2024
Teaching Slide Set

https://goldcopd.org/2024-gold-report/

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

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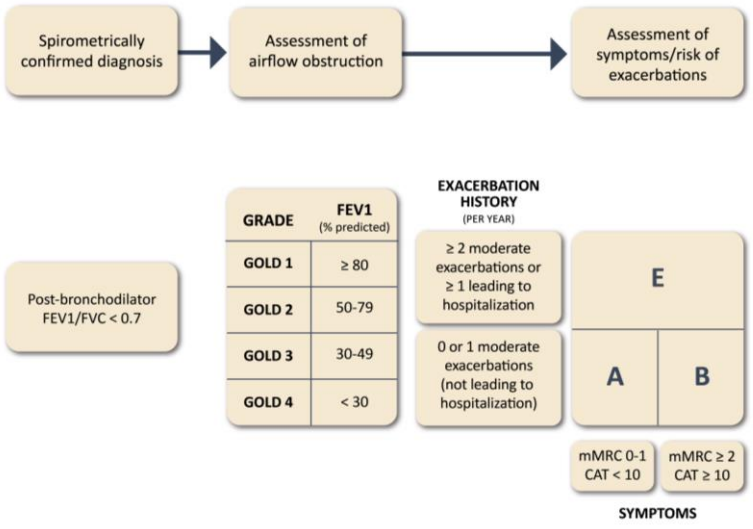
GOLD ABE Assessment Tool

Figure 2.10



2024 Teaching Slide Set

https://goldcopd.org/2024-gold-report/

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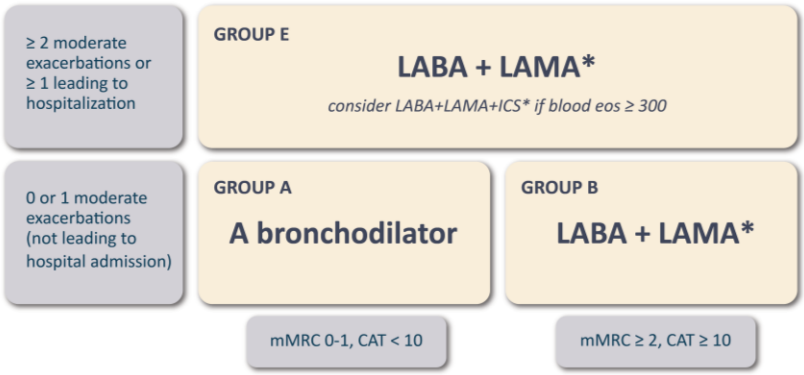
Initial Pharmacological Treatment

Figure 3.7



*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment

Exacerbations refers to the number of exacerbations per year; eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

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https://goldcopd.org/2024-gold-report/

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Bronchodilators in Stable COPD

Figure 3.19

2024 Teaching Slide Set

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Inhaled bronchodilators are recommended over oral bronchodilators **(Evidence A)**
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)** **albuterol/ipratropium - Combivent** vs. albuterol
- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea **(Evidence A)**, and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- When initiating treatment with long acting bronchodilators the preferred choice is a combination of a LABA and a LAMA. In patients with persistent dyspnea on a single long-acting bronchodilator treatment should be escalated to two **(Evidence A)**.
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)** **Umeclidinium/ Vilanterol (Anoro®), Tiotropium/Olodaterol (Stiolto®) QD** Glycopyrrolate/Formoterol (Bevespi®) and Glycopyrronium/Indacaterol (Ultibron®) BID
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**

https://goldcopd.org/2024-gold-report/

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Factors to Consider when Initiating ICS Treatment

Figure 3.21

2024 Teaching Slide Set

Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	History of hospitalization(s) for exacerbations of COPD[#] ≥ 2 moderate exacerbations of COPD per year[#] Blood eosinophils ≥ 300 cells/μL History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#] Blood eosinophils 100 to < 300 cells/μL
AGAINST USE	Repeated pneumonia events Blood eosinophils < 100 cells/μL History of mycobacterial infection

[#]despite appropriate long-acting bronchodilator maintenance therapy (see Figures 3.7 & 3.18 for recommendations); *note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

Adapted from & reproduced with permission of the © ERS 2019: *European Respiratory Journal 52 (6) 1801219; DOI: 10.1183/13993003.01219-2018 Published 13 December 2018*

https://goldcopd.org/2024-gold-report/

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Triple Inhaled LABA/LAMA/ICS Therapy

Google Images 2-10-2024

Fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation TRELEGY ELLIPTA ®
Once a day dosing
Cost: ~$630-735.00

Budesonide, glycopyrrolate, and formoterol fumarate inhalation aerosol **device BREZTRI AEROSPHERE®** -The inhaler device is bright yellow
-More accurate puff indicator means patients will know exactly how many doses they have left
-Upgraded cap designed to prevent unintended discharge of medicine
- **BID dosing**
Cost: ~$660-720.00

Google Images 2-10-2024

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Ensifentrine – Ohtuvayre by Verona Pharma

- **June 26, 2024 FDA approved ensifentrine (Ohtuvayre) a dual inhibitor of the phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4) enzymes, combines bronchodilator and non-steroidal anti-inflammatory properties in one compound to treat COPD in adults including chronic bronchitis, emphysema, or both.**, Verona says, differentiating it from existing drug classes used to treat COPD.
- Phase III clinical trials (**ENHANCE-1 and ENHANCE-2**). **Patients** aged 40–80 years **with moderate to severe symptomatic COPD were enrolled.** 760 (ENHANCE-1)and 789 (ENHANCE-2) patients were randomized and **treated with nebulized twice-daily ensifentrine 3 mg or placebo**, (69% and 55% receiving concomitant long-acting muscarinic antagonists or long-acting b2-agonists with or without ICS, respectively).
    - Am J Respir Crit Care Med Vol 208, Iss 4, pp 406–416, Aug 15, 2023

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Ensifentrine – Ohtuvayre

- **Ensifentrine treatment significantly improved average FEV1** area under the curve at 0–12 hours versus placebo(**ENHANCE-1, 87 ml** [95% confidence interval, 55, 119]; **ENHANCE-2, 94 ml** [65, 124]; both P , 0.001).
- **Ensifentrine treatment significantly improved symptoms (Evaluating Respiratory Symptoms) and quality of life (St. George's Respiratory Questionnaire) versus placebo at Week 24 in ENHANCE-1 but not in ENHANCE-2.**
- **Ensifentrine treatment reduced the rate of moderate or severe exacerbations versus placebo over 24 weeks by ~40% (ENHANCE-1, rate ratio, 0.64** [0.40, 1.00]; P = 0.050; **ENHANCE-2, rate ratio, 0.57** [0.38, 0.87]; P = 0.009) and **increased time to first exacerbation by ~40% (ENHANCE-1, hazard ratio, 0.62** [0.39,0.97]; P = 0.038; **ENHANCE-2, hazard ratio, 0.58** [0.38, 0.87];P = 0.009).
- **Adverse event rates were similar to those for placebo.**
  - Am J Respir Crit Care Med Vol 208, Iss 4, pp 406–416, Aug 15, 2023

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Ensifentrine – Ohtuvayre

- "**While the results of ENHANCE-1 and -2 are promising, there remains some uncertainty about the magnitude of overall benefit in patients receiving optimized modern inhaler therapies for COPD. We do not have significant concerns about harms with ensifentrine.** For these reasons, **we have high certainty that ensifentrine added to maintenance therapy, compared with maintenance therapy alone, results in at least a small net health benefit, and may result in substantial net health benefit ("B+")."**
- **Estimated cost ~ $1,500/month or $18,000/year**
- **"The exclusion of patients on LAMA/LABA therapy or on triple inhaler therapy raises questions about the benefits of ensifentrine when added on to some of the most recommended regimens."**
  - Draft Report - Ensifentrine for Chronic Obstructive Pulmonary Disease Institute for Clinical and Economic Review, 4/10/2024
  - https://icer.org/wp-content/uploads/2024/04/COPD_Draft-Report_For-Publication_04102024.pdf

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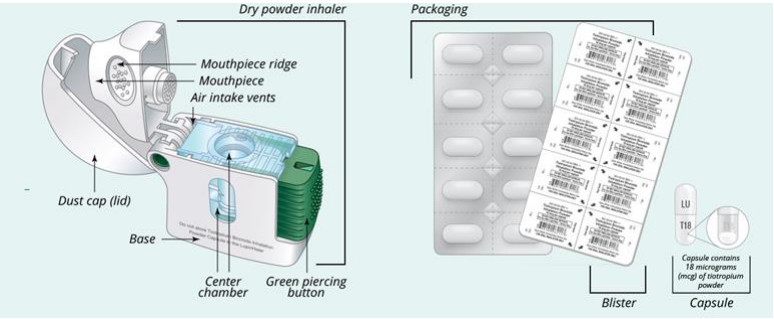
New Generic Tiotropium Bromide 18 mcg Capsule for Inhalation (Equivalent to Spiriva Handihaler)

August 16, 2023 - Lupin Launches Tiotropium Dry Powder Inhaler for the Treatment of COPD in the United States, the drug was **FDA approved on June 20, 2023. First FDA approved generic tiotropium bromide (AB rated).**



ttps://www.lupin.com/US/LupinHaler/

Cost: Spiriva Handihaler Brand 30 X 18 mcg capsules ~$523-573.00; Generic 30 X 18 mcg capsules ~$136 – 426.00 GoodRx 12-12-2023

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Cost of Inhalers for Asthma and COPD?

In January 2024, Senator Bernie Sanders and other Democratic lawmakers from the US Senate Committee on Health, Education, Labor, and Pensions (HELP Committee) sent letters to the top four manufacturers of inhalers sold in the U.S. — AstraZeneca, Boehringer, Teva Pharmaceuticals and GSK with concerns over high prices. The letters accused the companies of "manipulating the patent system" and of unfairly locking out generics from the market, driving up the cost of inhalers for Americans. The US Legislators also launched an investigation into the prices at which inhalers for asthma and chronic obstructive pulmonary disease were sold in the U.S. versus other countries.

https://www.sanders.senate.gov/press-releases/news-chairman-sanders-baldwin-lujan-markey-launch-help-committee-investigation-into-efforts-by-pharmaceutical-companies-to-manipulate-the-price-of-asthma-inhalers/

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Cost of Inhalers for Asthma and COPD?

March 7, 2024 – Boehringer Ingelheim announced it will cap out-of-pocket costs at $35 per month for eligible patients, including those who are uninsured or underinsured, for all the company's inhaler products, **starting June 1, 2024.**

Stiolto Respimat costs $627 in the US, and $69 in the UK.

March 18, 2024 - AstraZeneca announced it will cap out-of-pocket costs for its inhaled respiratory products at $35 per month for uninsured and underinsured patients in the US **starting June 1, 2024**.

Breztri Aerosphere costs $645 in the U.S. but $49 in the UK.

March 20, 2024 - GSK announced it will cap out-of-pocket costs for all its inhaled asthma and chronic lung disease medicines at $35 per month for eligible patients in the US, **starting Jan. 1, 2025.**

Trelegy Ellipta costs $658 in the US, and $57 in the UK.

https://www.sanders.senate.gov/press-releases/news-chairman-sanders-baldwin-lujan-markey-launch-help-committee-investigation-into-efforts-by-pharmaceutical-companies-to-manipulate-the-price-of-asthma-inhalers/

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Risk of Gastrointestinal Adverse Events Associated with Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss

A **random sample** of 16 million patients (2006-2020) **from the PharMetrics Plus database (IQVIA), a large health claims database that captures 93% of all outpatient prescriptions and physician diagnoses in the US** through the International Classification of Diseases, Ninth Revision (ICD-9) or ICD-10. In our cohort study, we **included new users of semaglutide or liraglutide, 2 main GLP-1 agonists, and the active comparator bupropion-naltrexone (Included 4144 liraglutide, 613 semaglutide, and 654 bupropion-naltrexone users).**

All GLP-1 agonist users had a record for obesity without diabetes, whether GLP-1 agonists were all used for weight loss is uncertain.

Table 2. Risks of Biliary Disease, Pancreatitis, Bowel Obstruction, and Gastroparesis Among Users of GLP-1 Agonists vs Bupropion-Naltrexone

	GLP-1 agonists, HR (95% CI)[a]		
Outcomes	Crude	Adjusted[b]	Bupropion-naltrexone
Primary analysis			
Biliary disease	1.48 (0.88-2.47)	1.50 (0.89-2.53)	1 [Reference]
Pancreatitis	10.33 (1.44-74.40)	9.09 (1.25-66.00)	1 [Reference]
Bowel obstruction	5.16 (1.27-21.00)	4.22 (1.02-17.40)	1 [Reference]
Gastroparesis	3.31 (1.04-10.50)	3.67 (1.15-11.90)	1 [Reference]

JAMA. Published online October 5, 2023. doi:10.1001/jama.2023.19574

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Hair Loss with Weight Loss Medications?

Temporary hair loss due to stress is known as telogen effluvium, where a physical stress to the body shocks the hair follicles, resulting in rapid shedding, and rapid weight loss no matter how achieved can cause the condition. In **the trials with semiglutide it was seen in ~3% of treated patients vs. ~1% with placebo and with terzepatide it was (7.1% female versus 0.5% male) and placebo (1.3% female versus 0% male) treatment groups.**

Telogen effluvium happens due to **hair follicles falling out when they don't get enough nutrition, having too little biotin, iron, protein, or zinc.**

There is generally a three-month lag after weight loss stops, when you hit a plateau, that the shedding will slowly start to dissipate, and hair will start to grow back.

You may be able to minimize the hair loss by making sure you get "adequate nutrition," including having plenty of protein in your diet.

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GLP-1 Agonists and Suicidal Ideation?

The U.S. **Food and Drug Administration has received 265 reports of suicidal thoughts or behavior in patients taking GLP-1 agonists since 2010**, Reuters found in an examination of the agency's adverse-event database. **Thirty-six of these reports describe a death by suicide or suspected suicide**. The FDA monitors such reports to help decide whether to further investigate a drug's safety and has taken action to protect patients, **mandating a warning label.**

March 8, 2024 FDA reviews of the clinical trials, including large outcome studies and observational studies, did not find an association between use of GLP-1 RAs and the occurrence of suicidal thoughts or actions.

https://www.fda.gov/drugs/fda-drug-safety-podcasts/update-fdas-ongoing-evaluation-reports-suicidal-thoughts-or-actions-patients-taking-certain-type#:~:text=Similarly%2C%20our%20reviews%20of%20the,of%20suicidal%20thoughts%20or%20actions.

April 12, 2024 The Pharmacovigilance Risk Assessment Committee (PRAC) safety committee of the European Medicines Agency (EMA) concluded the available evidence does not support a greater risk of suicidal or self-injurious thoughts and actions among users of glucagon-like peptide-1 (GLP-1) receptor agonists.

https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-8-11-april-2024

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FDA Postmarket Drug Safety Information – Semaglutide 5-22-2023

Can semaglutide be compounded?

When a drug is in shortage, compounders may be able to prepare a compounded version of that drug if they meet certain requirements in the Federal Food, Drug, and Cosmetic (FD&C) Act. As of May 2023, Ozempic and Wegovy are both listed on FDA's Drug Shortages list.

Are there concerns with compounded semaglutide?

FDA has received adverse event reports after patients used compounded semaglutide. Patients should not use a compounded drug if an approved drug is available to treat a patient. Patients and health care professionals should understand that the agency does not review compounded versions of these drugs for safety, effectiveness, or quality.

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/medications-containing-semaglutide-marketed-type-2-diabetes-or-weight-loss

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FDA Postmarket Drug Safety Information – Semaglutide 5-22-2023

The FDA has received reports that in some cases, **compounders may be using salt forms of semaglutide, including semaglutide sodium and semaglutide acetate. The salt forms are different active ingredients than is used the approved drugs, which contain the base form of semaglutide.** The **agency is not aware of any basis for compounding using the salt forms that would meet the FD&C requirements for types of active ingredients that can be compounded**. On April 27, 2023, FDA wrote to the National Association of Boards of Pharmacy expressing the agency's concerns with use of the salt forms in compounded products.

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/medications-containing-semaglutide-marketed-type-2-diabetes-or-weight-loss

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Compounded Semaglutide On-line

- **Ro, founded in 2017, was initially called Roman and originally sold drugs for treating erectile dysfunction. Since then, it has expanded rapidly including weight loss drugs like compounded semaglutide.**
  - https://www.theverge.com/23878992/ro-ozempic-subway-ads-telehealth-weight-loss-drugs
- **Hims & Hers Health, one of the online pharmacies that also got its start prescribing erectile dysfunction medications, is now offering knockoff versions of GLP-1 weight loss drugs**. Hims & Hers says it will offer drugs **that mimic Ozempic and Wegovy, the active ingredient of which is semaglutide.**
- The copycat versions are made by compounding pharmacies. The formulations aren't the same as the FDA-approved versions of the drug and haven't been directly evaluated by the FDA, either. But they're cheaper than the real thing: **$199 a month, compared to the branded version, which can cost more than $1,000 a month without insurance.**
  - **The company added "a record 172,000 net new subscribers," it said in its shareholder letter. The company has splashed out on TV advertising during NBA and NFL games as well as Keeping Up With the Kardashians and The Bachelorette.**
- **Compounding pharmacies can make knockoff versions of branded drugs when they are in shortage, as the GLP-1 drugs** — prescribed for diabetes and weight loss — currently are. The FDA has already received reports of adverse events for compounded versions of semaglutide.
  - https://www.theverge.com/2024/5/20/24160884/hims-hers-ozempic-weight-loss-wegovy-pharmacy

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Compounded Semaglutide

Updated **May 30, 2024- As part of its ongoing commitment to patient safety, Novo Nordisk has filed 9 new lawsuits and is seeking to add claims to two existing lawsuits against several medical spas, weight loss clinics, compounding pharmacies, and other companies to protect US patients and consumers from unlawful marketing and sales of compounded drugs claiming to contain semaglutide, which pose significant safety risks to patients.**

As of March 31, 2024, the FDA Adverse Event Reporting System (FAERS) data includes **442 cases of adverse events associated with compounded drugs claiming to contain semaglutide. Of those cases, 319 were classified as "serious" adverse events, 99 reported hospitalization, and 7 involved death.**

The latest round of legal actions is based on alarming new evidence collected by Novo Nordisk on the practices and products being sold by these entities. Some of these include:

Mounting evidence of high levels of known impurities and the presence of unknown impurities in injectable compounded products claiming to contain semaglutide, potentially exposing patients to significant health risks

Compounded products that claim to contain semaglutide, but have been shown to contain no semaglutide whatsoever based on the results of testing

False claims that the compounded drugs are FDA-approved

False claims that these products are sourced from and/or are equivalent to Novo Nordisk's FDA-approved semaglutide medicines.

Potentially dangerous advertisements by retailers on "how to make your own" injectable semaglutide at home and sales of "semaglutide" products without any prescription from a medical professional

https://www.novonordisk-us.com/media/news-archive.html

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Compounded Tirzepatide

May 14, 2024, Lilly Update on Mounjaro® and Zepbound® (tirzepatide) Compounding Litigation

- **Following a series of lawsuits Eli Lilly and Company filed in September and October 2023, Lilly has entered into a settlement agreement requiring defendant Totality Medispa to make a monetary payment and prohibiting Totality from engaging in certain conduct. Lilly's settlement will stop Totality Medispa from misleading consumers into believing that this med spa is selling Mounjaro® or Zepbound® approved by the FDA, that its compounded products have been the subject of clinical tests, or that its compounded medicines have been proven safe and effective to achieve certain clinical results.**
  - **The settlement agreement requires Totality Medispa to make a monetary payment and to take several corrective actions. Totality must:**
  - **Only obtain and distribute compounded tirzepatide products that are produced in compliance with U.S. federal law;**
  - **Report to FDA any adverse events that patients experience after using Totality's compounded tirzepatide;**
  - **Display on its website and all advertisements that "Compounded versions of tirzepatide are not FDA-approved, and neither the FDA nor any global regulatory agency has reviewed these products for safety, quality, or efficacy;"**
  - **Not make any statements suggesting its products are genuine, FDA-approved Lilly products; and**
  - **No longer use Lilly branding in the promotion of any of its products.**
    - https://investor.lilly.com/news-releases/news-release-details/lilly-update-mounjaror-and-zepboundr-tirzepatide-compounding#:~:text=Display%20on%20its%20website%20and,%2C%20quality%2C%20or%20efficacy%3B%E2%80%9D

67

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

- **Metabolic dysfunction-associated steatotic liver disease (MASLD; formerly termed nonalcoholic fatty liver disease; NAFLD)** is a clinico-histopathologic entity with histologic features that resemble alcohol-induced liver injury, but by definition, it **occurs in patients with little or no history of alcohol consumption.** It encompasses a histologic spectrum that **ranges from fat accumulation in hepatocytes without concomitant inflammation or fibrosis (simple hepatic steatosis) to hepatic steatosis with a necroinflammatory component (steatohepatitis) that may or may not have associated fibrosis. The latter condition, referred to as metabolic dysfunction-associated steatohepatitis (MASH; formerly termed nonalcoholic steatohepatitis; NASH) may progress to cirrhosis in up to 20 percent of patients. MASH is now recognized to be a leading cause of cryptogenic cirrhosis.**
- MASLD is seen worldwide with an estimated **prevalence of 30 percent among the general population and with higher prevalence in males compared with females (40 versus 26 percent). NAFLD remains the second leading indication for liver transplantation in the United States and is estimated to become the leading cause.**
  - UpToDate accessed 6-9-2024

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Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

- **Risk factors and associated conditions** — Patients with MASLD have at least one metabolic risk factor:
  - Obesity, defined as BMI ≥25 kg/m2 (or BMI ≥23 kg/m2 for Asian individuals)
  - Hypertension
  - Dyslipidemia
  - Type 2 diabetes mellitus
- **Treatment: General measures for all patients**
  - **Abstain from alcohol – We suggest that patients refrain from alcohol.**
  - **Immunizations – Vaccination for hepatitis A virus and hepatitis B virus should be given to patients without serologic evidence of immunity. Additional vaccines for patients with chronic liver disease include pneumococcal vaccination and standard immunizations that are given to the general population (eg, influenza, diphtheria, tetanus boosters)**
  - **Modify risk factors for cardiovascular disease – Patients with MASLD are at increased risk for cardiovascular disease and often have multiple risk factors for cardiovascular disease (eg, hypertension, dyslipidemia). and associated conditions').**
  - **Management of patients with MASLD and diabetes includes optimization of blood glucose control.**
  - **Most patients with MASLD who have dyslipidemia are candidates for lipid-lowering therapy.**
  - **Weight loss — Weight loss is the primary therapy for most patients with MASLD.**
    - UpToDate accessed 6-9-2024

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Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

- **Drug Treatment (UpToDate 6-9-2024) We may use a GLP-1 receptor agonist (off-label) for patients with biopsy-proven MASH with fibrosis stage ≥F2 who do not achieve weight loss with lifestyle interventions.** We typically begin a GLP-1 receptor agonist (eg, semaglutide, liraglutide) with the same dosing that is used for the labeled indication (obesity). **We titrate the dose to achieve a weight loss goal of 7 to 10 percent of body weight. For such patients, we also continue to promote lifestyle interventions as long-term therapy.**
- **We anticipate using resmetirom, a thyroid hormone receptor-beta agonist, for patients with MASH and fibrosis stage F2 or F3 who do not achieve sustained weight loss**. Additional studies will help inform the role of resmetirom in clinical practice. Patients with cirrhosis were excluded from published clinical trials, but ongoing trials are evaluating safety and efficacy of resmetirom in such patients.
  - UpToDate accessed 6-9-2024

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Changes in Liver and Abdominal Fat in Tirzepatide-Treated Patients Achieving Normoglycemia in the SURPASS-3 MRI Sub-study

Tirzepatide (TZP), a once-weekly GIP/GLP-1 receptor agonist, **significantly reduced liver fat content (LFC) and volumes of visceral and abdominal subcutaneous adipose tissue (VAT and ASAT) vs insulin degludec in a subpopulation of patients in the SURPASS-3 phase 3 trial.** This post-hoc analysis evaluated changes from baseline to Week 52 in these outcomes and other clinical and laboratory parameters in TZP-treated patients achieving or not achieving normoglycemia (HbA1c <5.7%) at Week 52.

Among patients achieving HbA1c <5.7% and ≥5.7%, respectively, 56% and 27% achieved Liver Fat Content <6%, and 91% and 64% achieved ≥30% reduction in Liver Fat Content.

Subset of patients achieving at Week 52	HbA_{1c} <5.7% (N=70)		HbA_{1c} ≥5.7% (N=118)	
	Baseline and change from baseline at Week 52 (LSM ± SE)			
Liver fat content [a], %	16.96 ± 1.06	-10.36 ± 0.64	15.00 ± 0.82	-5.51 ± 0.49
VAT volume [a], L	6.23 ± 0.25	-2.26 ± 0.17	7.04 ± 0.19	-1.00 ± 0.13
ASAT volume [a], L	10.77 ± 0.54	-2.81 ± 0.23	10.53 ± 0.40	-1.40 ± 0.18
Weight [b], kg	96.65 ± 1.95	-14.07 ± 0.72	96.09 ± 1.50	-7.28 ± 0.56
HbA_{1c} [b], %	7.99 ± 0.10	-2.88 ± 0.08	8.44 ± 0.08	-1.83 ± 0.07

Diabetes 2023;72(Supplement_1):758-P

71

GLP-1 Agonists and Fatty Liver?

August 2023 Novo Nordisk awarded a $9.57 million grant supporting the SAMARA clinical trial at the University of California San Diego NAFLD Research Center to **evaluate the use of semaglutide in patients with fibrosis due to nonalcoholic fatty liver disease.**

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Still to Come?

The **first triple receptor (GLP-1, GIP, and glucagon) agonist, Retatrutide investigational by Eli Lilly,** demonstrated promising weight loss potential this year. Glucagon receptor agonism, in addition to well-known counterregulatory responses to hypoglycemia, results in consumption of smaller meal sizes and in increased energy expenditure, making it a potential target for weight loss, particularly when used in dual or triple receptor agonism with GLP-1 and/or GIP.

Retatrutide (LY3437943; Eli Lilly) is a single peptide conjugated to a fatty diacid moiety and has agonism toward the GIP, GLP-1, and GCG receptors. As compared with the endogenous receptor ligands, retatrutide is less potent at the human GCG and GLP-1 receptors (by a factor of 0.3 and 0.4, respectively) and is more potent at the human GIP receptor (by a factor of 8.9). The pharmacokinetics of retatrutide are considered dose-proportional; it has a **half-life of approximately 6 days, which enables weekly sub Q administration.**

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Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

A **phase 2, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of retatrutide in adults without diabetes but with obesity or overweight plus ≥1 weight-related condition.**

Intervention: **338 adults 18 to 75 years of age with a body-mass index (BMI) of 30 to 50 or a BMI of 27 to <30 plus ≥1 weight-related condition were assigned to receive subcutaneous retatrutide with the dose adjusted to reach one of four maintenance doses (2, 4, 8, and 12 mg) or placebo once weekly for 48 weeks.** All participants also took part in a lifestyle intervention. The primary end point was the percentage change in weight from baseline to 24 weeks.

N Engl J Med 2023; 389:514-526

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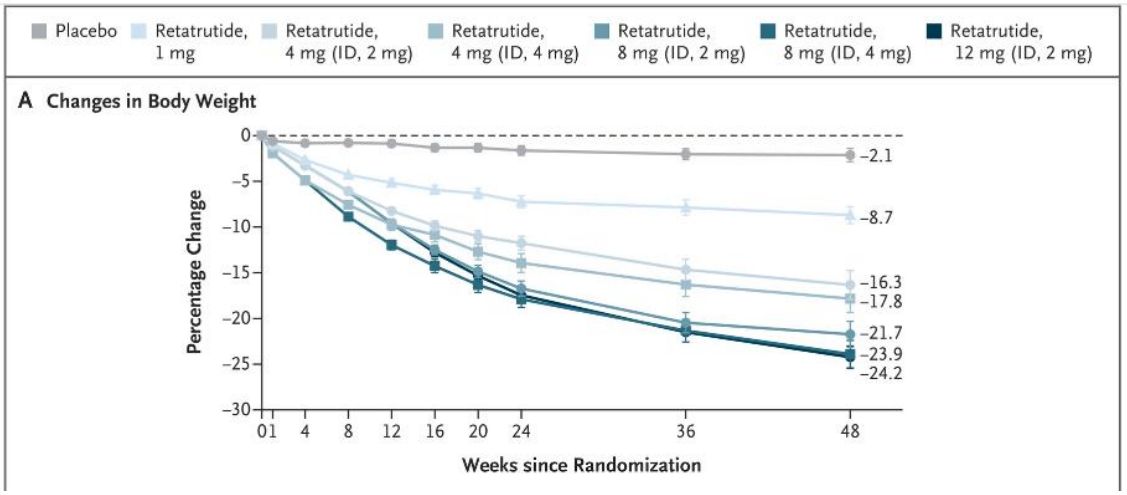
Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial



N Engl J Med 2023; 389:514-526

75

Retatrutide and Fatty Liver Disease?

Fatty liver disease, now called metabolic dysfunction-associated steatotic liver disease or MASLD. Patients have MASLD **when fat accounts for 5% or more of their livers' weight and at least one of five cardiometabolic risk factors, such as stroke, heart attack and diabetes.**

Ninety-eight obese adults between 18 and 75 years old were randomly assigned a retatrutide dose **in the Phase 2 trial. At week 48, the relative decrease in liver fat was 81.7% among those taking 8mg doses of retatrutide, and 86% for those taking 12mg. Reductions of liver fat to less than 5% occurred in 89% of the 8mg group and 93% of the 12mg group at week 48.** The 48-week liver study demonstrated an average weight loss of 23.8% and 25.9% for patients taking 8mg and 12mg of retatrutide, respectively.

The research **findings show retatrutide could become a "bottom up" therapy for at-risk patients, preventing liver disease from progressing and possibly reversing it.**

Terzepatide research has shown it also has the ability to improve liver health by reducing liver fat.

Arun Sanyal, M.D., director of the VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, shared these findings on Nov. 13, 2023, at a meeting of the American Association for the Study of Liver Diseases in Boston.

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Resmetirom – Rezdiffra by Madrigal Pharmaceuticals

March 14, 2024, the U.S. Food and Drug Administration granted Breakthrough Therapy, Fast Track and Priority Review and Accelerated Approval of resmetirom (Rezdiffra), the first medication for the treatment of adults with noncirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced liver scarring (fibrosis), to be used along with diet and exercise. (Label does not require liver biopsy like clinical trial).

The accelerated approval pathway, allows for earlier approval of drugs that treat serious conditions and address an unmet medical need, based on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit.

Resmetirom is a partial activator of a thyroid hormone receptor primarily THR-β; stimulation of THR-β in the liver reduces intrahepatic triglycerides, whereas actions of thyroid hormone outside the liver, including in heart and bone, are largely mediated through THR-α.

https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-scarring-due-fatty-liver-disease

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Resmetirom – Rezdiffra

The safety and efficacy of resmetirom was evaluated based on an analysis of a surrogate endpoint at month 12 in a 54-month, randomized, double-blind placebo-controlled MAESTRO-NASH Clinical Trial. The **surrogate endpoint measured the extent of liver inflammation and scarring.** The **sponsor is required to** conduct a post-approval study to verify and describe resmetirom's clinical benefit, which will be done through **completing the same 54-month study, which is still ongoing**. To enroll in the trial, **patients needed to have a liver biopsy showing inflammation due to NASH with moderate or advanced liver scarring**. In the trial, **888 subjects were randomly assigned to receive one of the following: placebo (294 subjects); 80 milligrams of resmetirom (298 subjects); or 100 milligrams (296 subjects); once daily**, in addition to standard care for NASH, which includes counseling for healthy diet and exercise.

https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-scarring-due-fatty-liver-disease

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Resmetirom – Rezdiffra

At 12 months, liver biopsies showed that a greater proportion of subjects who were treated with resmetirom achieved NASH resolution or an improvement in liver scarring as compared with those who received the placebo.

A total of **26% to 27% of subjects who received 80 mg of resmetiron and 24% to 36% of subjects who received 100 mg experienced NASH resolution and no worsening of liver scarring, compared to 9% to 13% of those who received placebo and counseling on diet and exercise.**

The range of responses reflects different pathologists' readings.

Use of resmetirom should be avoided in patients with decompensated cirrhosis. Patients should stop using resmetirom if they develop signs or symptoms of worsening liver function while on treatment.

- https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-scarring-due-fatty-liver-disease

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Resmetirom – Rezdiffra

Pharmacokinetics:

Resmetirom median terminal plasma **half-life (t½) is 4.5 hours.**

Resmetirom is **metabolized by CYP2C8** and is not metabolized by other CYP enzymes in vitro.

No clinically significant differences in the pharmacokinetics of resmetirom were observed based on age (18 to 83 years), sex, or race.

Resmetirom is an inhibitor of CYP2C8. **Avoid gemfibrozil and reduce dose of resmetirom with clopidogrel a CYP 2C8 inhibitor.**

Glucuronidation Enzymes: Resmetirom is an inhibitor of UDP-glucuronosyltransferases (UGTs) 1A4 and 1A9. The clinical relevance of UGT1A4 and UGT1A9 inhibition is unknown.

Transporters: Resmetirom is a substrate for organic anion-transporting polypeptides (OATP) 1B1 and 1B3 (**avoid cyclosporine**) and breast cancer resistance protein (BCRP). **Statins: Rosuvastatin and simvastatin: Limit daily statin dosage to 20 mg. Pravastatin and atorvastatin: Limit daily statin dosage to 40 mg.**

https://www.madrigalpharma.com/wp-content/uploads/2024/03/Prescribing-Information.pdf

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Resmetirom – Rezdiffra

Table 1: Exposure-Adjusted Incidence Rates (EAIR) of Common Adverse Reactions Reported with REZDIFFRA in Adult Patients with Noncirrhotic NASH (Trial 1)[a, b, c]

Adverse Reaction	Placebo N=294 n (EAIR[d])	REZDIFFRA 80 mg Once Daily N=298 n (EAIR[d])	REZDIFFRA 100 mg Once Daily N=296 n (EAIR[d])
Diarrhea	52 (14)	78 (23)	98 (33)
Nausea	36 (9)	65 (18)	51 (15)
Pruritus	18 (4)	24 (6)	36 (10)
Vomiting	15 (4)	27 (7)	30 (8)
Constipation	18 (4)	20 (5)	28 (8)
Abdominal pain	18 (4)	22 (5)	27 (7)
Dizziness	6 (1)	17 (4)	17 (4)

d. The EAIR per 100 PY can be interpreted as an estimated number of first occurrences of the adverse reaction of interest if 100 patients are treated for one year.

Gallbladder-Related Adverse Reactions : A higher incidence of cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) was observed in the treatment arms compared to placebo. However, the EAIRs for these events were less than 1 per 100 PY for all treatment arms.

https://www.madrigalpharma.com/wp-content/uploads/2024/03/Prescribing-Information.pdf

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Resmetirom – Rezdiffra

Liver Enzymes: the **mean elevation in ALT and AST values was less than 1.5 times baseline at 4 weeks after treatment initiation. These values returned to baseline around 8 weeks after initiating treatment.**

Thyroid Function Tests: a **decrease in levels of prohormone free T4 (FT4) of mean 2%, 13%, and 17% was seen at 12 months in patients treated with placebo, resmetirom 80 mg once daily, and 100 mg once daily, respectively,** with **minimal changes in active hormone T3 or in TSH. There were no clinical findings associated with FT4 decreases.**

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Resmetirom – Rezdiffra

Dosage: The **recommended dosage of resmetirom is based on actual body weight**. For patients weighing:

- **<100 kg, the recommended dosage is 80 mg orally once daily.**
- **≥100 kg, the recommended dosage is 100 mg orally once daily.**

Administer resmetirom **with or without food**.

Cost: **60, 80 and 100 mg tablets $47,400.00 per year**

The **Institute for Clinical and Economic Review** (ICER) has calculated a **health-benefit price benchmark** (HBPB) **of $39,600–$50,100 per year for resmetirom**, which is used to treat nonalcoholic steatohepatitis (NASH).
https://icer.org/wp-content/uploads/2022/10/NASH-Final-Report_For-Publication_053023.pdf

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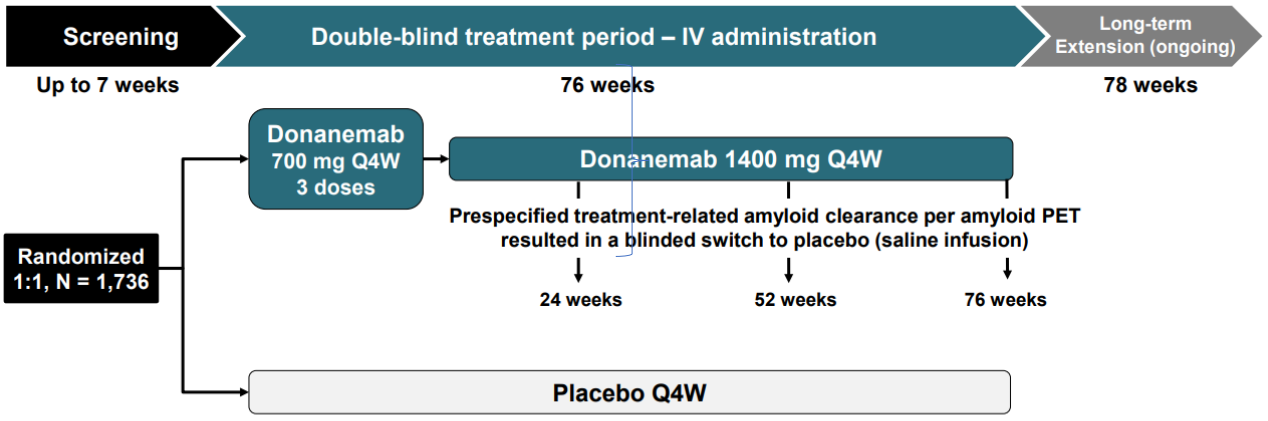
Donanemab – Kisunla by Eli Lilly

- **July 2, 2024, the US Food and Drug Administration granted full clinical approval to Eli Lilly to market donanemab, brand name Kisunla, for the treatment of early Alzheimer's disease, including Mild Cognitive Impairment (MCI) or mild dementia. The FDA granted this application Fast Track, Priority Review and Breakthrough Therapy designations.**
- **Approval is primarily based upon the TRAILBLAZER-ALZ 2 Trial in 1736 participants with early symptomatic Alzheimer's disease and amyloid and tau pathology who were randomized to either donanemab or placebo infused every 4 weeks for 72 weeks.**
  - JAMA 2023;330(6):512-527

84

CO-15

Phase 3 Study AACI Design

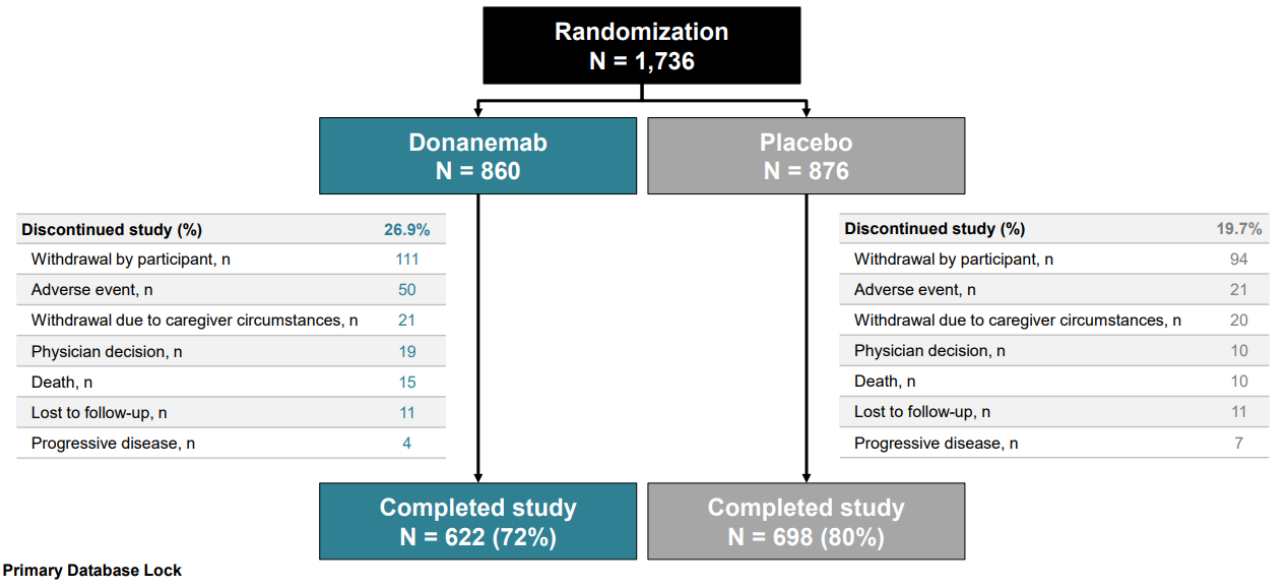


Stratification
- Investigative site
- Tau pathology (low-med vs high by PET)

*Dose switched to placebo when amyloid PET levels were < 11 Centiloids on and visit or between 11 and 25 on two consecutive PET scans

85

AACI: Patient Disposition



Discontinued study (%)	26.9%
Withdrawal by participant, n	111
Adverse event, n	50
Withdrawal due to caregiver circumstances, n	21
Physician decision, n	19
Death, n	15
Lost to follow-up, n	11
Progressive disease, n	4

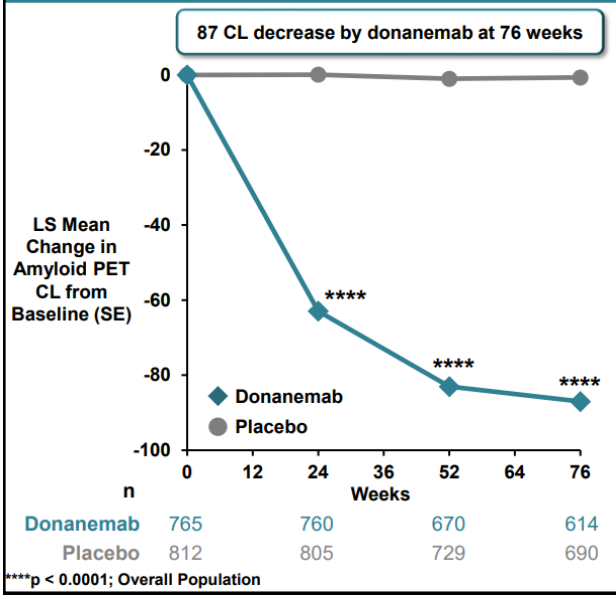
Discontinued study (%)	19.7%
Withdrawal by participant, n	94
Adverse event, n	21
Withdrawal due to caregiver circumstances, n	20
Physician decision, n	10
Death, n	10
Lost to follow-up, n	11
Progressive disease, n	7

Primary Database Lock

86

CO-29

Amyloid Clearance and Effect in Disease-Relevant Biomarkers Support Donanemab in All Baseline Tau Participant Groups



****p < 0.0001; Overall Population

Percent change from baseline at 76 weeks	No / Very-Low Tau†	Low – Medium Tau	High Tau
Amyloid reduction	86%	85%	80%
P-tau217 reduction	56%	39%	33%
GFAP reduction	22%	21%	18%

†Data from AACI addendum

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Primary and Secondary Outcomes

- **The primary efficacy endpoint was change in the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. The iADRS is a combination of two scores: the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog13) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living (ADCSiADL) scale**. The total score ranges from 0 to 144, with lower scores reflecting worse cognitive and functional performance.
- **The change threshold on the iADRS associated with clinically meaningful worsening has been estimated to be 5 points for patients with MCI due to AD and 9 points for patients with AD with mild dementia.**
- Other efficacy endpoints included Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), ADAS-Cog13, and ADCS-iADL.

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Minimal Clinically Important Differences for Cognitive Outcomes

Table 3.2. Minimal Clinically Importance Differences for Cognitive Outcomes

Cognitive Outcome	Minimal Clinically Important Difference (MCID)
Clinical Dementia Rating – Sum of Boxes (CDR-SB)	Change of 0.98-1.63 for MCI due to AD and mild AD dementia.[36]
Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog), including ADAS-Cog-13 and ADAS-Cog14.	Change of 2 points for MCI due to AD[37] and ≥3 points for mild AD.[38,39]
Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version) (ADCS-MCI-ADL)	There are no data on MCID.
AD Composite Score (ADCOMS)	There are no data on MCID.

AD: Alzheimer's Disease, MCI: Mild cognitive impairment

MCID refers to changes within a specific patient. Aggregate measures, such as mean change in an outcome, will potentially obscure changes in individual patients that are above or below the MCID. It would be helpful in assessing magnitude of benefit relative to clinical benefit if manufacturers provide analyses of the percentage of patients who experience decreases in an outcome measure beyond a prespecified endpoint.

Alzheimer's Disease – Evidence Report

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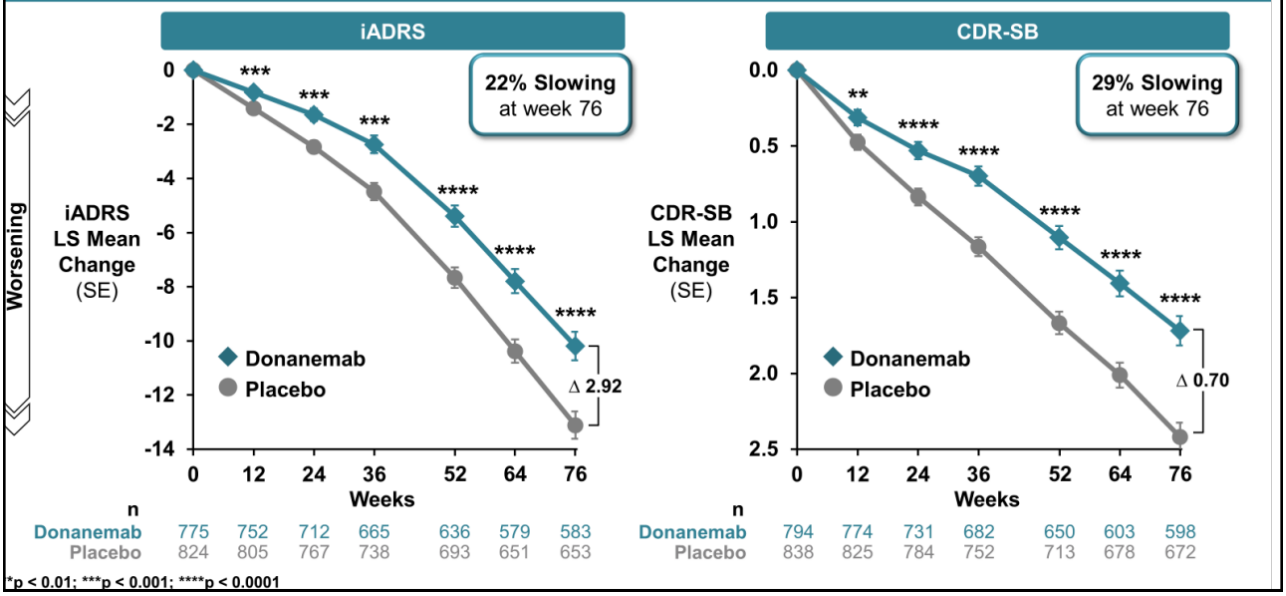
Significant Slowing of Clinical Progression for Primary and Key Secondary Endpoint (Overall Population)

CO-23



n							
Donanemab	775	752	712	665	636	579	583
Placebo	824	805	767	738	693	651	653

n							
Donanemab	794	774	731	682	650	603	598
Placebo	838	825	784	752	713	678	672

*p < 0.01; ***p < 0.001; ****p < 0.0001

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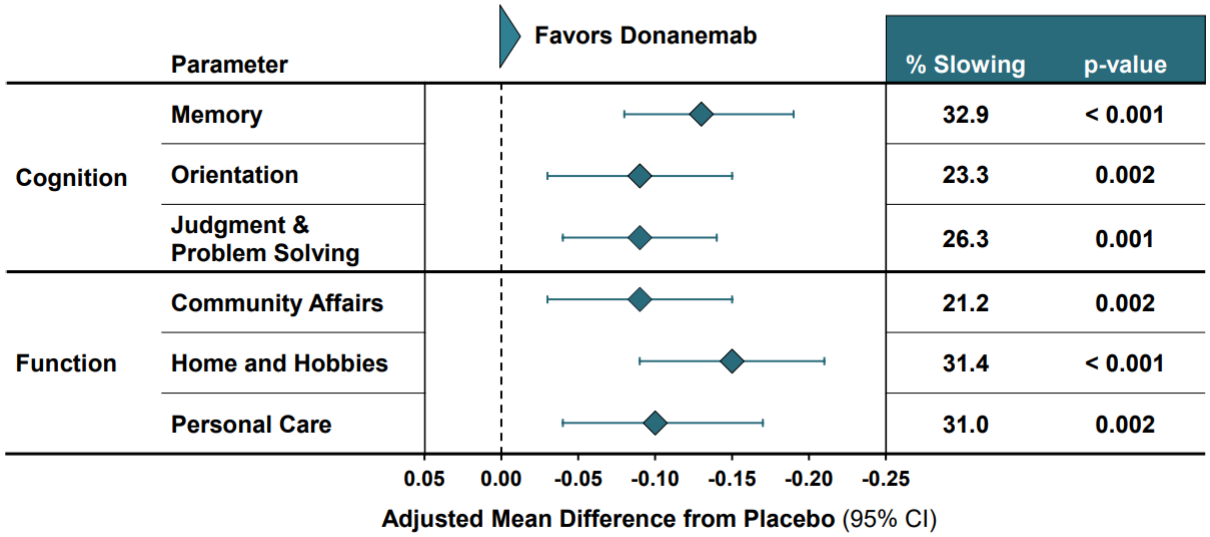
Clinically Relevant Treatment Effect Across CDR-SB Domains at 76 Weeks (Overall Population)

CO-25

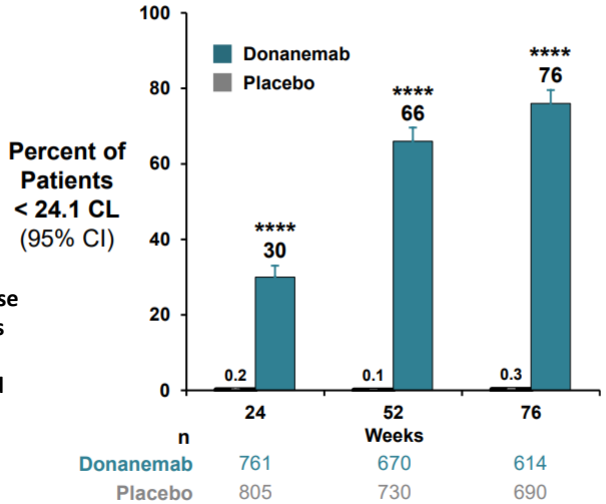


91

High Levels of Treatment-Related Amyloid Clearance Support Limited-Duration Dosing

CO-31

The proportion of subjects meeting dose stopping criteria was 17%, 42%, and 60%, at Weeks 24, 52, and 76, respectively



76% reached treatment-related amyloid clearance by 76 weeks

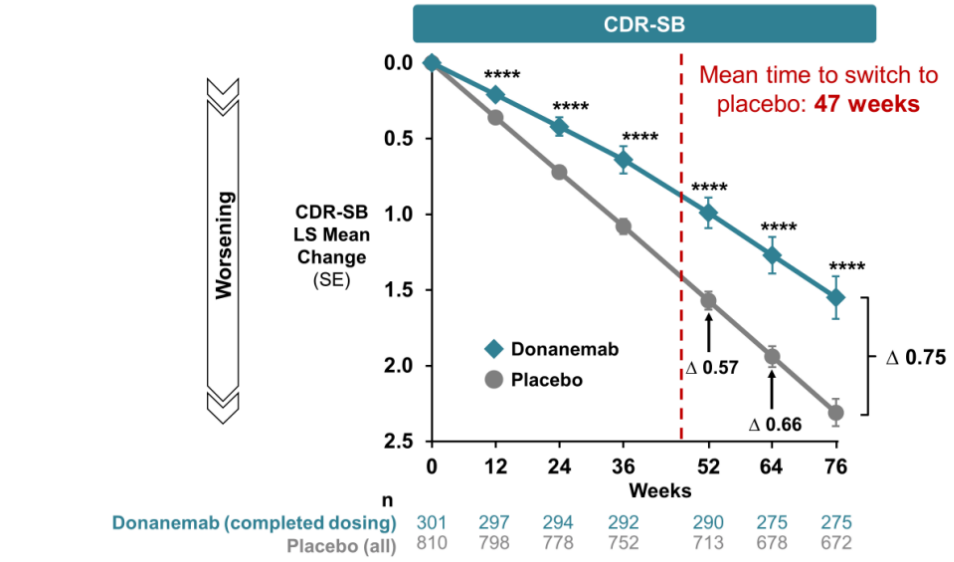
- 29% of donanemab-treated subjects entering long-term extension were still receiving 1400 mg dose
- Upon dose cessation, amyloid began to re-accumulate at a mean rate of 2.8 Centiloids/year

****p < 0.0001; Overall Population

92

CO-32

Widening Between Group Difference after Treatment Completion Supports Limited Duration Dosing

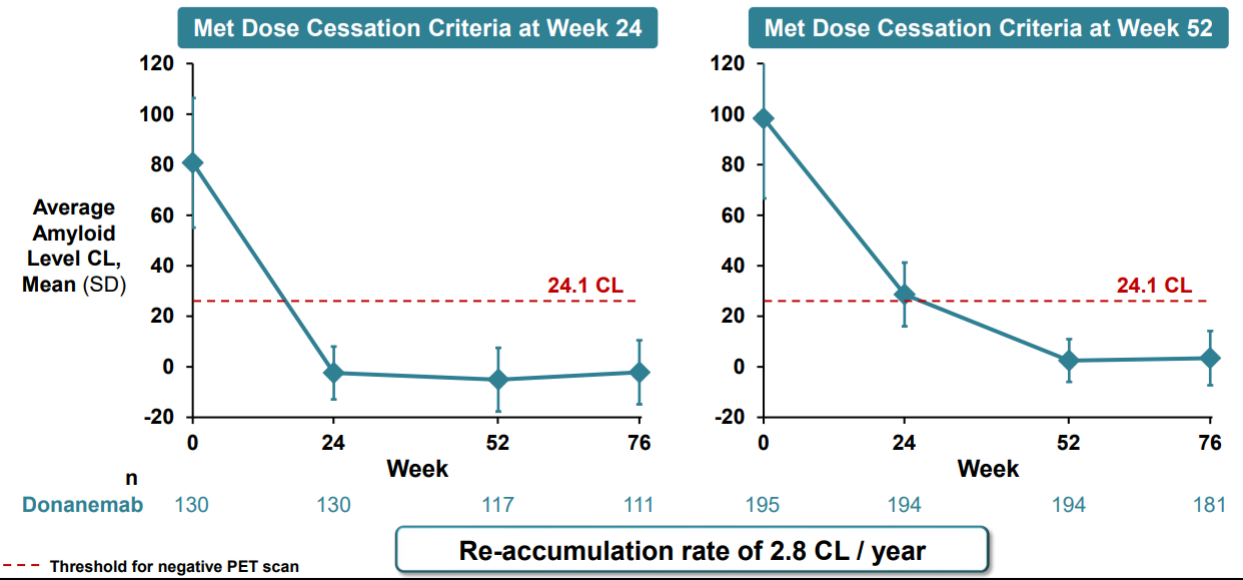


****p < 0.0001; Overall Population

93

CO-33

Amyloid Levels Remain Low After Treatment Related Amyloid Clearance



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CO-42

Common AEs (≥ 5% of Patients)

Preferred Term	Dona-PC		All Dona
	Donanemab N = 984	Placebo N = 999	Donanemab N = 2,802
Any AE	89%	83%	81%
ARIA-E*	24%	2%	20%
ARIA-H**	18%	7%	17%
COVID-19	14%	16%	15%
Fall	13%	13%	12%
Headache	13%	10%	11%
Infusion related reaction	9%	0.4%	8%
Superficial siderosis of central nervous system	8%	1%	6%
Dizziness	7%	6%	6%
Urinary tract infection	6%	7%	6%
Arthralgia	6%	5%	4%
Nausea	5%	4%	3%

*Amyloid-related imaging abnormality – oedema/effusion; **Amyloid-related imaging abnormality – microhemorrhages and hemosiderin deposits

95

CO-43

Overview of ARIA

Preferred term, n (%)	DONA-PC		All Dona
	Donanemab N = 984	Placebo N = 999	All Dona N = 2,802
ARIA-E	240 **(24%)**	19 **(2%)**	571 **(20%)**
SAE	15 **(2%)**	0	34 **(1%)**
Treatment discontinuations	28 **(3%)**	4 **(0.4%)**	54 **(2%)**
Symptomatic	57 **(6%)**	1 **(0.1%)**	127 **(5%)**
ARIA-H	309 **(31%)**	130 **(13%)**	778 **(28%)**
SAE	4 **(0.4%)**	0	9 **(0.3%)**
Treatment discontinuations	22 **(2%)**	4 **(0.4%)**	42 **(1.5%)**
Symptomatic	10 **(1%)**	3 **(0.3%)**	15 **(0.5%)**
Intracerebral hemorrhage > 1 cm	3 **(0.3%)**	2 **(0.2%)**	10 **(0.4%)**
SAE	1 **(0.1%)**	1 **(0.1%)**	3 **(0.1%)**
Treatment discontinuations	2 **(0.2%)**	1 **(0.1%)**	6 **(0.2%)**

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Black Box Warning

- **ApoE ε4 Homozygotes Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including Kisunla, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers.**
- **Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.** Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results.
- **An FDA-authorized test for detection of ApoE ε4 alleles to identify patients at risk of ARIA if treated with Kisunla is not currently available. Currently available tests used to identify ApoE ε4 alleles may vary in accuracy and design**

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Patients/Caregivers Should Know

- **Healthcare providers should be aware that ARIA can present with focal neurologic symptoms that can mimic stroke.**
- Patients who develop symptoms concerning for stroke may require a more extensive evaluation and MRI to assess the etiology of the symptoms.
- **Patients should carry a medical information card indicating that they are being treated with donanemab**.

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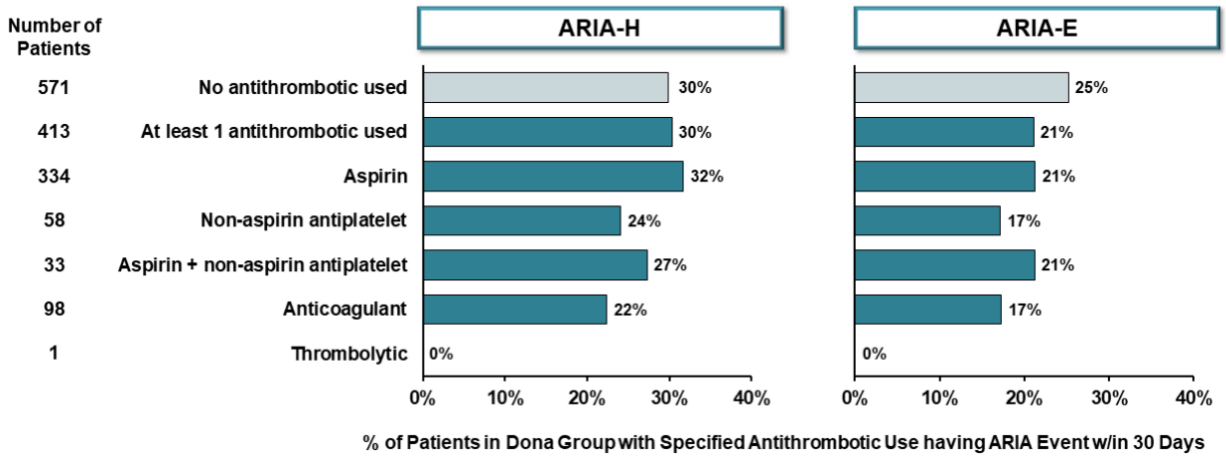
Antithrombotics Did Not Increase Risk for ARIA

10% of Donanemab patients used anticoagulants, 40% used anti-platelets in Dona-PC



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Donanemab - Kisunla

Dosage and Administration:

- **Confirm the presence of amyloid beta pathology prior to initiating treatment with a baseline MRI.**
- **The recommended dosage of donanemab is 700 mg administered as an intravenous infusion over approximately 30 minutes every four weeks for the first three doses, followed by 1400 mg every four weeks.**
- **Consider stopping dosing with donanemab based on reduction of amyloid plaques to minimal levels on amyloid PET imaging.**
- **Obtain an MRI prior to the 2nd, 3rd, 4th, and 7th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms.**

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Donanemab - Kisunla

- **Available in 350 mg/20 mL (17.5 mg/mL) single-dose vial**
- **Cost $695.65/ 350 mg vial (each dose is 2 or 4 vials/Q 4 weeks)**
- **First 3 doses $1391.30, then $2782.60 per dose until discontinued. (Note 60% of patients were able to dicontinue therapy by 76 weeks in the Trailblazer Trial based upon amyloid PET levels)**
- **Cost for 76 weeks or 19 doses ($4173.90 first 12 weeks and $44,521.60 for last 16 weeks, total $48,695.50 for 76 weeks of treatment plus cost of MRIs).**

According to the Alzheimer's Association the average out of pocket cost for an amyloid PET scan is $3,000.00 or more,

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Clinically Important Benefits and Harms of Monoclonal Antibodies Targeting Amyloid for the Treatment of Alzheimer Disease: A Systematic Review and Meta-Analysis

- **19 publications with 23,202 total participants that evaluated 8 anti-amyloid antibodies. There were small improvements over placebo in the Alzheimer's Disease Assessment Scale (ADAS)-Cog-11 to -14 score** (standardized mean difference = −0.07; 95% CI, −0.10 to −0.04), **Mini Mental State Examination score** (0.32 points; 95% CI, 0.13 to 0.50), and **Clinical Dementia Rating-Sum of Boxes scale score** (mean difference =−0.18 points; 95% CI, −0.34 to −0.03), **and the combined functional scores** (standardized mean difference = 0.09; 95% CI, 0.05 to 0.13). **None of the changes, including those for lecanemab, aducanumab, and donanemab, exceeded the minimal clinically important difference (MCID).**
  - **"We focused very clearly on patient-centered outcomes,"** said Ebell, who is a physician and professor of epidemiology and biostatistics in UGA's College of Public Health. **"We found that even after 18 to 24 months of treatment, the differences in function and cognition between treated and untreated patients were so small that a patient or their caregiver generally wouldn't notice the difference,"** said Ebell.
    - The Annals of Family Medicine January 2024, 22 (1) 50-62; DOI: https://doi.org/10.1370/afm.3050

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