Immunization Update

New Zoster sub-unit Vaccine (Shingrix) by GSK

- FDA approved for adults age 50 and above Oct 20, 2017
- ZOE-50 Trial: a randomized, observer-blind, placebo-controlled, multi-center, multinational phase III efficacy study designed to assess HZ/su (herpes zoster/sub-unit vaccine) in 16,160 patients age 50 and older.
  - viral protein (gE) combined with the adjuvant system - AS01B (a liposome-based adjuvant system containing immunoenhancers) (Not a live attenuated vaccine)
  - 2-dose schedule at 0 and 2 months.
  - Cost ~$280.00 for the 2 doses [zoster vaccine live (Zostavax) – cost ~ $230.00]
  - The vaccine efficacy (defined as the reduction in disease incidence in the vaccinated group compared to the unvaccinated group) in adults 50 years and older was 97.2%, compared to placebo.
  - Study 110390. 2014. Available at: http://www.gsk-clinicalstudyregister.com/ *

HZ/su (herpes zoster/sub-unit vaccine) - Shingrix

- In ZOE-70 Trial: 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%).

Shingles Vaccine Persistence

<table>
<thead>
<tr>
<th>Vaccine efficacy against HZ for ZVL and HZ/su, by year following vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
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</table>

Shingles Vaccines

<table>
<thead>
<tr>
<th>Vaccine efficacy, 50-59</th>
<th>ZVL</th>
<th>HZ/su</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine efficacy, 60-69</td>
<td>97%</td>
<td>64%</td>
</tr>
<tr>
<td>Vaccine efficacy, 70-79</td>
<td>91%</td>
<td>43%</td>
</tr>
<tr>
<td>Vaccine efficacy, ≥ 80 years</td>
<td>93%</td>
<td>18%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine efficacy against HZ</th>
<th>By 4 years</th>
<th>By 6 years</th>
<th>By 9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZVL</td>
<td>95%</td>
<td>85%</td>
<td>75%</td>
</tr>
<tr>
<td>HZ/su</td>
<td>91%</td>
<td>67%</td>
<td>57%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Administration</th>
<th>ZVL</th>
<th>HZ/su</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM, 2 doses</td>
<td>95%</td>
<td>60%</td>
</tr>
<tr>
<td>IM, 1 dose</td>
<td>93%</td>
<td>53%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Storage</th>
<th>ZVL</th>
<th>HZ/su</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerator</td>
<td>Freezer</td>
<td>Freezer</td>
</tr>
<tr>
<td>Reactogenicity</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Immune compromised</td>
<td>No recommendation</td>
<td>Limited role</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>No recommendation</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>ACP age recommendation</td>
<td>50 and older</td>
<td>60 and older</td>
</tr>
<tr>
<td>ACP recommendation</td>
<td>Preferred</td>
<td>Option</td>
</tr>
</tbody>
</table>
HZ/su (herpes zoster/sub-unit vaccine) - Shingrix

### Table 5. Efficacy of SHINGRIX on Overall Incidence of Postherpetic Neuralgia Compared with Placebo in Studies 1 and 2 (Pooled Data) (mTYC)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>N</th>
<th>n</th>
<th>Incidence Rate of PHN* per 1,000 Person-Years</th>
<th>N</th>
<th>n</th>
<th>Incidence Rate of PHN per 1,000 Person-Years</th>
<th>% Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (0-79)</td>
<td>8,250</td>
<td>4</td>
<td>0.1</td>
<td>8,346</td>
<td>36</td>
<td>1.2</td>
<td>88.8 (68.7, 97.1)</td>
</tr>
<tr>
<td>70 - 79</td>
<td>6,468</td>
<td>2</td>
<td>0.1</td>
<td>6,554</td>
<td>29</td>
<td>1.2</td>
<td>93.0 (72.5, 99.2)</td>
</tr>
<tr>
<td>≥80</td>
<td>1,782</td>
<td>2</td>
<td>0.3</td>
<td>1,792</td>
<td>7</td>
<td>1.1</td>
<td>71.2 (51.5, 87.1)</td>
</tr>
</tbody>
</table>

N = Number of subjects included in each group; n = Number of subjects having at least 1 PHN; CI = Confidence Interval.

ACIP Meeting Vote 10-25-2017

- The CDC’s Advisory Committee on Immunization Practices voted on Wednesday to recommend use of the newly approved herpes zoster vaccine, HZ/su (Shingrix).
- The inactivated, recombinant subunit, two-dose vaccine was recommended in a 12-to-1 vote for adults aged 50 years and older. The other shingles vaccine on the market, ZVL (Zostavax), is recommended only for those aged 60 and older.
- Here are some of the data presented to the committee:
  - HZ/su (Shingrix) had 97% efficacy in those aged 50–69 and 91% efficacy in older adults.
  - Efficacy was at least 85% at 4 years post-vaccination in patients aged 70 and older.
  - Thirteen people in their 50s—and 11 in their 60s—would need to be vaccinated to prevent one zoster case.
  - HZ/su (Shingrix) was more efficacious than ZVL (Zostavax), particularly for older adults.
- The committee also voted to recommend HZ/su (Shingrix) for patients who’ve previously received Zoster Vaccine Live (ZVL) (Zostavax) with at least 8 weeks between vaccines. The vote to recommend HZ/su (Shingrix) over ZVL (Zostavax) narrowly passed by 8 to 7. Dissenters expressed concerns about supply, unknown long-term safety issues, and lack of head-to-head comparisons.

ACIP/CDC Recommendations

- ACIP approved the following recommendations by majority vote at its October 2017 meeting:
  - **Use of Herpes Zoster subunit vaccine (Shingrix) for the prevention of herpes zoster and its related complications for immunocompetent adults 50 years of age and older;**
  - **Use of Herpes Zoster subunit vaccine for immunocompetent adults who previously received Zoster Vaccine Live (Zostavax) at least 2 months after Zoster Vaccine Live (Zostavax); and**
  - **Preference for Herpes Zoster subunit vaccine over Zoster Vaccine Live.**

- Fluzone High-Dose was 24.2% more effective in preventing influenza in 32,000 adults aged 65 years or older than regular Fluzone in a large-scale 2 year clinical trial conducted in the US and Canada, vaccine maker Sanofi Pasteur told the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention today.
- The rate of laboratory-confirmed influenza among participants receiving Fluzone High-Dose was 1.43% compared with 1.89% among patients immunized with Fluzone. For the FDA to deem Fluzone High-Dose as superior, the vaccine needed to demonstrate a relative efficacy rate of at least 9.1%. It achieved a rate more than twice that — **RRR = 24.2%, ARR = 0.46%, NNT = 218**
Flu in older patients?

- Why is there a need for new flu vaccines designed specifically for people 65 years of age and older?
  - CDC studies conducted during previous flu seasons estimate that 80 to 90 percent of seasonal flu-related deaths and 50-70 percent of hospitalizations occur among people 65 years of age and older. However, older adults with weaker immune systems also may have a lower protective immune response after flu vaccination compared to younger, healthier people. This can result in lower vaccine effectiveness (i.e., a measure of how well the flu vaccine protects against flu illness), in these people. Newer flu vaccines made specifically for people 65 years of age attempt to improve the immune response and protection provided by flu vaccination in this age group.

Adjuvant Flu Vaccine – Flud

- Flud, which is manufactured using an egg-based process, is formulated with the adjuvant MF59, an oil-in-water emulsion of squalene oil. Squalene, a naturally occurring substance found in humans, animals and plants, is highly purified for the vaccine manufacturing process.
  - Adjuvants are incorporated into some vaccine formulations to enhance or direct the immune response of the vaccinated individual.

Adjuvant Flu Vaccine – Flud

- Are there increased benefits of FLUAD™ compared to unadjuvanted seasonal flu vaccines for this age group?
  - Studies that have tested Flud's ability to generate an immune response against an influenza virus (immunogenicity) have found that antibody levels were comparable to levels induced by unadjuvanted trivalent seasonal flu vaccines (e.g., Agriflu). However, an observational study conducted in Canada among adults 65 years of age and older during the 2011-2012 flu season found that FLUAD™ was significantly more effective in preventing laboratory-confirmed influenza compared with an unadjuvanted standard-dose inactivated influenza vaccine.
  - Does FLUAD™ offer better protection than the high-dose flu vaccine?
    - To date, there have been no randomized studies comparing FLUAD™ with Fluzone High-Dose vaccine.
      - CDC 12-2017

Adjuvant Flu Vaccine – Flud

- In individuals 65 years of age and older. In that trial, 7,082 participants received either Flud or Agriflu. The study showed that Flud induced antibody levels that were comparable to the levels induced by Agriflu.
- Safety was also evaluated in approximately 27,000 additional individuals 65 years of age and older. No safety concerns were identified with Flud. The most common adverse events reported include injection site pain and tenderness, muscle aches, headache and fatigue.

Improved LAIV strain selection identified a new H1N1 strain that is more immunogenic in children

- LAIV is not recommended in the US as H1N1 vaccine strains used in 2013-2014 and 2015-2016 had reduced effectiveness
  - A broad-based scientific investigation determined that H1N1 LAIV strains used in those seasons replicate less well compared to older more effective LAIV strains
  - Assays measuring replicative fitness were incorporated into strain selection for 2017-2018 and a new H1N1 strain (A/Slovenia) selected
  - A clinical trial was conducted in US children to determine if new A/Slovenia strain was more immunogenic compared to previous A/Bolivia strain used in 2015-2016
  - In the study, the new A/Slovenia H1N1 strain induced antibody responses that were significantly higher than those seen with the A/Bolivia strain (Immune responses were similar to those seen with a highly effective pre-pandemic LAIV H1N1 strain)
  - Clinical study results validate improved strain selection process
- New strain selection process applied to all future LAIV strains and data reviewed by FDA/EMA annually.
- The new LAIV Quadrivalent FluMist was recommended for the 2018-19 season
  - ACIP Meeting Feb 21, 2018
AAP recommends Injectable Flu Vaccines over LAIV

• 5/21/2018 The American Academy of Pediatrics said that it will recommend the injectable influenza vaccine over the live attenuated flu vaccine (nasal spray marketed as FluMist) for youth when it publishes its formal policy statement on flu prevention in September.

• The AAP says the nasal spray should be used only if children would otherwise go unvaccinated. A member of the AAP Committee on Infectious Diseases said, "If you get the nasal spray vaccine, just be aware that there might be a chance you will not be fully protected against H1N1 strains of flu. The efficacy of this new formulation has not yet been determined."

Vaccines Approved for Children 6 mo and older for 2017-18

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Dosage</th>
<th>Age</th>
<th>Mercury</th>
<th>Protein</th>
<th>Latex</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluarix</td>
<td>GlaxoSmithKline</td>
<td>0.5 mL prefilled syringe</td>
<td>6 months</td>
<td>NR</td>
<td>≥6 months</td>
<td></td>
<td>IM</td>
</tr>
<tr>
<td>FluLaval</td>
<td>ID Biomedical Corp. of Quebec</td>
<td>0.5 mL prefilled syringe</td>
<td>6 months</td>
<td>≤&lt;25</td>
<td>≥6 months</td>
<td></td>
<td>No IM</td>
</tr>
<tr>
<td>Fluzone</td>
<td>Sanofi Pasteur</td>
<td>0.25 mL prefilled syringe</td>
<td>6 through 35 months</td>
<td>NR</td>
<td>6 through 35 months</td>
<td></td>
<td>IM</td>
</tr>
</tbody>
</table>

HPV9 Vaccine – Gardasil-9 by Merck

• December 10, 2014 The FDA approved nine-valent HPV vaccine (V503) Gardasil-9 that includes coverage for 6, 11, 16, and 18—just like HPV4—but also for five additional high cancer-risk strains: 31, 33, 45, 52, and 58.

-- What might it offer vs. the current vaccines?
• Additional 25% CIN 2 or cervical lesions
• Additional 18% vaginal cancer cases
• Additional 15% cervical cancer cases
• Additional 4% of oropharyngeal cancer cases

• The FDA has stated that "Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers."

ACIP Meeting 10-19-2016

• The ACIP recommended that 11- to 12-year-olds receive 2 doses of human papillomavirus (HPV) vaccine at least 6 months apart rather than the previously recommended 3 doses to protect against cancers caused by HPV infections. Teens and young adults who start the series later, at ages 15 through 26 years, will continue to need 3 doses of HPV vaccine to protect against cancer-causing HPV infection.

• October 7, 2016, the FDA approved adding a 2-dose schedule for 9-valent HPV vaccine (Gardasil 9) for adolescents aged 9 through 14 years

HPV-9 Vaccine

• What is the recommendation for persons with immunocompromising conditions?
• CDC recommends 3 doses of HPV vaccine (0, 1–2, 6 months) for immunocompromised people age 9 through 26 years.

• People whose immune responses might be lower, for example due to HIV infection, cancer, autoimmune disease, or taking immunosuppressant medications, should receive 3 doses to make sure they get the most benefit.

• However, children with asthma, diabetes, and other conditions that would not suppress immune response to HPV vaccination can receive a 2-dose schedule.

New Data on 10 Year Effectiveness of Quadravalent HPV Vaccine

• Ten years after 9-15 year old girls and boys received the 3 doses of quadravalent HPV vaccine, researchers measured the participants’ antibodies and level of immunity against each of the strains in the vaccine, HPV 6, 11, 16 and 18. They also looked at how many of the participants had a disease or ongoing infection caused by these HPV types.

• Strength of immune response against HPV types 6, 11 and 16 ranged from 89-99%, depending on the strain and ranged from 77-79% against HPV 18. These numbers indicate seropositivity and do not represent vaccine effectiveness, which is much higher.

• Those who received the vaccine between ages 9-12 had approximately 16% to 42% higher levels of antibodies (titers) 10 years later than those who had gotten the vaccine at ages 13-15.
New Data on 10 Year Effectiveness of Quadrivalent HPV Vaccine

- None of the participants had diseases from any of the four HPV types in the vaccine. Ten of them, however, did have an infection lasting at least 6 months involving one of the four strains, and two participants had an infection lasting at least a year.
- None of the participants showed any side effects or other adverse events throughout those 10 years.
- “These findings justify efforts to vaccinate subjects at the earliest opportunity,” wrote Daron Ferris, MD, a professor of obstetrics and gynecology at Augusta University in Augusta, Georgia, and his colleagues. “Moreover, by vaccinating preadolescents before exposure to HPV, the full potential of the vaccine is more likely to be realized.”


Tdap in Pregnancy Update 2017

- The recommendation to vaccinate mothers, including adolescent mothers, as early as possible in the 27- to 36-week gestational window. The words “as early as possible” were added because evidence shows that when the immunization is given closer to 27 weeks, “the baby is born with a higher concentration of maternal antibodies.
- The most severe complications for pertussis occur in the first 2 months of a child’s life, yet infants cannot receive the pertussis vaccine before 2 months of age.

— MMWR February 10, 2017 / 66(5);136–138

Hepatitis B Update 2017

- New with this schedule is that one dose of the monovalent hepatitis B vaccine is recommended for all newborn children within 24 hours of birth.
  - Previously, a birth dose was recommended, but that was interpreted to mean the first couple of weeks of life.
  - “There are about 25,000 babies a year born to mothers who are chronically infected with hepatitis B. We know that the risk of transmission to a baby from a mother chronically infected can be as high as 90%. And we know, if babies are infected at birth, they have a significant risk of developing cirrhosis or cancer of the liver.”

— MMWR February 10, 2017 / 66(5);136–138

Heplisav-B (HepB-CpG) Vaccine

- 4-20-2018 MMWR: On February 21, 2018, the Advisory Committee on Immunization Practices (ACIP) recommended Heplisav-B (HepB-CpG), a yeast-derived vaccine prepared with a novel adjuvant, administered as a 2-dose series (0, 1 month) for use in persons aged ≥18 years.
- The ACIP Hepatitis Vaccines Work Group conducted a systematic review of the evidence, including data from four randomized controlled trials assessing prevention of HBV infection and six randomized controlled trials assessing adverse events in adults. Seroprotective antibody to hepatitis B surface antigen (anti-HBs) levels were achieved in 90.0%–100.0% of subjects receiving HepB-CpG (Dynavax Technologies Corporation), compared with 70.3%–90.2% of subjects receiving Engerix-B (GlaxoSmithKline Biologicals). The benefits of protection with 2 doses administered over 1 month make HepB-CpG an important option for prevention of HBV.

— MMWR February 10, 2017 / 66(5);136–138

HPV-9 Vaccine

- October 5, 2018 the FDA approved Gardasil-9 (Human Papillomavirus [HPV] 9-valent Vaccine, Recombinant) expanding the approved use of the vaccine to include women and men aged 27 through 45 years of age.
- In approximately 3,200 women 27 through 45 years of age, followed for an average of 3.5 years, Gardasil was 88 percent effective in the prevention of a combined endpoint of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to HPV types covered by the vaccine.
- Data in men is based upon immunogenicity data from a clinical trial in which 150 men, 27 through 45 years of age, received a 3-dose regimen of Gardasil over 6 months.
- The ACIP is scheduled to meet and review the data on October 25, 2018.

— MMWR February 10, 2017 / 66(5);136–138

Heplisav-B (HepB-CpG) Vaccine

- On November 9, 2017, Heplisav-B (HepB-CpG), a single-antigen HepB vaccine with a novel immunostimulatory sequence adjuvant, was approved by the Food and Drug Administration for the prevention of HBV in persons aged ≥18 years. The vaccine is administered as 2 doses, 1 month apart.
- HepB-CpG is the third inactivated HepB vaccine currently recommended for use in the United States to join Engerix-B or Recombivax HB which both require 3 doses.
Heplisav-B (HepB-CpG) Vaccine

- The 2-dose HepB vaccine series only applies when both doses in the series consist of HepB-CpG. Series consisting of a combination of 1 dose of HepB-CpG and a vaccine from a different manufacturer should consist of 3 total vaccine doses and should adhere to the 3-dose schedule minimum intervals of 4 weeks between dose 1 and 2, 8 weeks between dose 2 and 3, and 16 weeks between dose 1 and 3. Doses administered at less than the minimum interval should be repeated.

- Data are limited on the safety and immunogenicity effects when HepB-CpG is interchanged with HepB vaccines from other manufacturers. When feasible, the same manufacturer's vaccines should be used to complete the series. However, vaccination should not be deferred when the manufacturer of the previously administered vaccine is unknown or when the vaccine from the same manufacturer is unavailable.

Adults who are recommended to receive hepatitis B vaccine

- Persons at risk for infection through sexual exposure
  - Sex partners of hepatitis B virus (HBV)–infected persons
  - Sexually active persons in a long-term, mutually-monogamous relationship
  - Persons seeking evaluation or treatment for a sexually transmitted infection

- Persons at risk for infection by percutaneous or mucosal exposure to blood
  - Men who have sex with men
  - Persons seeking evaluation or treatment for a sexually transmitted infection
  - International travelers to countries with high or intermediate levels of endemic HBV infection
  - Persons at risk for infection by percutaneous or mucosal exposure to blood
  - Men who have sex with men
  - Persons seeking evaluation or treatment for a sexually transmitted infection

- Persons with a history of current or recent injection drug use

- Persons with a history of injection drug use

- Persons seeking evaluation or treatment for a sexually transmitted infection

- Persons with human immunodeficiency virus infection (COR III harm/LOE EO)

- Men who have sex with men

- Persons with human immunodeficiency virus infection (COR III harm/LOE EO)

- Persons seeking evaluation or treatment for a sexually transmitted infection

- Postvaccination

Heplisav-B (HepB-CpG) Vaccine

- Postvaccination serologic testing. To assess response to vaccination and the need for revaccination, postvaccination serologic testing 1–2 months after the final dose of vaccine is recommended for certain persons following vaccination (e.g., hemodialysis patients, HIV-infected and other immunocompromised persons, health care personnel, and sex partners of HBsAg-positive persons). Postvaccination serologic testing should be performed using a method that allows determination of the protective level of anti-HBs (≥10 mIU/mL). Persons with anti-HBs <10 mIU/mL following receipt of 2 doses of HepB-CpG should be revaccinated. Revaccination may consist of administration of a second complete HepB vaccine series followed by anti-HBs testing 1–2 months after the final dose. Alternatively, revaccination may consist of administration of an additional single HepB vaccine dose followed by anti-HBs testing 1–2 months later (and, if anti-HBs remains <10 mIU/mL, completion of the second HepB vaccine series followed again by anti-HBs testing 1–2 months after the final dose). Administration of more than two complete HepB vaccine series is generally not recommended, except for hemodialysis patients.

New Focused Update on New Pharmacologic Therapy for Heart Failure

- Recommendation for ARNI (angiotensin receptor – nephrilysin inhibitor) i.e., valsartan/sacubitril - Entresto

  - “The clinical strategy of inhibition of the renin angiotensin system with ACE inhibitors (COR 1/LOE A) or ARB (COR 1/LOE A) or ARNI (COR 1/LOE B-Randomized) in conjunction with evidence-based beta blockers and aldosterone antagonists in selected patients is recommended for patients with chronic HFrEF to reduce morbidity and mortality”


New Focused Update on New Pharmacologic Therapy for Heart Failure

  - “In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (COR 1/LOE B-R)

  - “ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.” (COR III Harm/LOE B-R)

  - “ARNI should not be administered to patients with a history of angioedema” (COR III harm/LOE CO)


Valsartan/Sacubitril – Entresto Safety Concern

- The November 1, 2017 edition of ISMP QuarterWatch, a publication from the Institute for Safe Medication Practices, reports that a so-called “drug safety signal” has been detected recently for valsartan/sacubitril (Entresto) as regards hypotension being a serious side effect which warrants more attention — and, perhaps, an increased warning.

- Relying upon “New data from 2017 Q1” of the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), this leading drug safety publication ends its recent report on valsartan/sacubitril (Entresto) with these statements in the final Conclusions section:
Valsartan/Sacubitril – Entresto Safety Concern

• ISMP identified 1,684 adverse event reports indicating a hypotension-related event (ranging from dizziness to blackouts with some requiring hospitalization), more than for any other cardiovascular drug we monitored over the 12 months ending in 2017 Q1. They occurred in older patients (median age 70 years), and although there were 69 reported deaths, in two-thirds of the cases, the health consequences were not severe.
• The FDA has not yet made any label changes.

How many patients with HFrEF are receiving Guideline Directed Medical Therapy?

• The CHAMP-HF (Change the Management of Patients with Heart Failure) registry included outpatients in the United States with chronic HFrEF receiving at least 1 oral medication for management of HF.
• 3,518 patients from 150 primary care and cardiology practices were included. Mean age was 66 +/- 13 years, 29% were female, and mean EF was 29 +/- 8%.
• Among eligible patients, 27%, 33%, and 67% were not prescribed ACEI/ARB/ARNI, beta-blocker, and MRA therapy, respectively.
• Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACEI/ARB/ARNI, beta-blocker, and MRA.
  – (J Am Coll Cardiol 2018;72:351–66)

Starting and Target Doses of Select Guideline-Directed Medical Therapy for Heart Failure

2018 ADA Standards of Medical Care in Diabetes

Highlights related to drug therapy:

• Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A1C >10% and/or blood glucose levels>300mg/dL. E
• Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C>9%. E
• In patients without atherosclerotic cardiovascular disease, if monotherapy or dual therapy does not achieve or maintain the A1C goal over 3 months, add an additional antihyperglycemic agent based on drug-specific and patient factors. A
  – Diabetes Care 2018;41(Suppl. 1):S73–S85

2018 ADA Standards of Medical Care in Diabetes

• A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, history of atherosclerotic cardiovascular disease, impact on weight, potential side effects, renal effects, delivery method (oral versus subcutaneous), cost, and patient preferences. E
• In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors. A*
  – Canagliflozin may be considered to reduce major adverse cardiovascular events, based on drug-specific and patient factors. C* (Black Box Warning Risk of amputations, also warning about increase risk of fractures with canagliflozin)
  – Diabetes Care 2018;41(Suppl. 1):S73–S85

2018 ADA Standards of Medical Care in Diabetes

• Continuous reevaluation of the medication regimen and adjustment as needed to incorporate patient factors and regimen complexity is recommended. E
• For patients with type 2 diabetes who are not achieving glycemic goals, drug intensification, including consideration of insulin therapy, should not be delayed. B
• Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated. A
  – Diabetes Care 2018;41(Suppl. 1):S73–S85
New ADA/EASD Guidance on Diabetes

- The treatment approach to type 2 diabetes should begin with an assessment of cardiovascular disease (CVD) status, other comorbidities, and patient preferences, according to a draft of the upcoming 2018 joint consensus statement from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). The guideline will be presented on October 5, 2018 at the EASD annual meeting in Berlin and will be published in Diabetes Care and Diabetologia.

New ADA/EASD Guidance on Diabetes

- In general, the ADA/EASD document will advise assessment of cardiovascular status as the first step in determining treatment approach. Separate algorithms will address patients with atherosclerotic cardiovascular disease (ASCVD) and those with heart failure.

New ADA/EASD Guidance on Diabetes

- Lifestyle modification and metformin are still considered the cornerstones of treatment, although the panel did debate the ongoing role of metformin as the first-line pharmacologic therapy. Ultimately they opted to stick with the recommendation for now because of low cost and proven safety and efficacy.

New ADA/EASD Guidance on Diabetes

- Then, for patients in whom ASCVD predominates, a GLP-1 receptor agonist with proven CVD benefit or SGLT2 inhibitor with proven CVD benefit (provided the patient has adequate kidney function) are recommended, in that order.

New ADA/EASD Guidance on Diabetes

- The order is reversed in patients for whom heart failure predominates: listed first is an SGLT2 inhibitor with evidence of reducing heart failure in a cardiovascular outcomes trial (if the patient has adequate kidney function), with a GLP-1 receptor agonist with proven CVD benefit as an alternative option.

New ADA/EASD Guidance on Diabetes

- "They were careful to discuss the limitations of the evidence." Her "personal favorites" were the caveat that "beyond dual therapy is an evidence-free zone," and the emphasis that the cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists have only been proven in patients with established CVD.

New ADA/EASD Guidance on Diabetes

- She also particularly liked the "stop light" graphics indicating which medications should be stopped or reduced once other drugs are added, noting, "This is a common question I get from primary care providers about therapy intensification."
Empagliflozin – Jardiance New Indication

December 2, 2016

• The U.S. Food and Drug Administration today approved a new indication for Jardiance (empagliflozin) to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.

• Based on a post market Empa Reg Outcome trial of more than 7,000 patients with type 2 diabetes and cardiovascular disease.

  In the trial, Jardiance was shown to reduce the risk of cardiovascular death compared to a placebo when added to standard of care therapies for diabetes and atherosclerotic cardiovascular disease.

EMPAREG OUTCOME Trial

• The primary outcome (CV mortality, non-fatal MI and non-fatal stroke) occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority).

  -- ARR = 1.6%, NNT 63
  -- No significant differences in rates of MI or CVA
  -- No significant difference with 10 vs. 25 mg doses.
  -- Death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction; ARR = 2.2%, NNT 46

  * NEJM on-line 9-17-2015

EMPAREG OUTCOME Trial

• Hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction)

• Death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction).

• Among patients receiving empagliflozin, there was an increased rate of genital infection (1 in 20 or 5%) but no increase in other adverse events.

  -- NEJM on-line 9-17-2015
Canagliflozin: CANVAS and CANVAS R Trials

- Integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk (65.6% had a history of ASCVD). Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks (3.62 years).
- The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (3 point MACE).
  - Initially tested for non-inferiority (p=0.001) and then if appropriate for superiority (p=0.02)

Canagliflozin: CANVAS and CANVAS R Trials

- Diabetic ketoacidosis: 0.6/1000 pt. yrs. vs. 0.3 (p=0.14 NS)
- Amputations: 6.3/1000 pt. yrs. vs. 3.4 (p=0.001) NNH = ~56
- Fractures (all): 15.4/1000 pt. yrs. vs. 11.9 (p=0.02) NNH = ~286
- Volume depletion: 26/1000 pt. yrs. vs. 18.5 (p=0.009) NNH = ~140
- Infection of male genitalia: 34.9/1000 pt. yrs. vs. 10.8 (p<0.001)
- Female mycotic genital infection: 68.8/1000 pt. yrs. vs. 17.5 (p=0.001) NNH = ~19

New FDA Safety Alert

- [5-16-2017]: “Based on new data from two large clinical trials (CANVAS and CANVAS-R), the FDA has concluded that the type 2 diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) causes an increased risk of leg and foot amputations. We are requiring new warnings, including our most prominent Boxed Warning, to be added to the canagliflozin drug labels to describe this risk.”
  - Before initiating canagliflozin, consider factors in the patient’s history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.

Declare-TIMI-58 Trial

- Dapagliflozin effect on cardiovascular events A multicenter, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes
- A Phase III cardiovascular (CV) outcomes trial (CVOT) for Farxiga (dapagliflozin), the broadest SGLT2 inhibitor CVOT conducted to date. The trial evaluated the CV outcomes of dapagliflozin vs. placebo over a period of up to five years, across 53 countries and in more than 17,000 adults with type 2 diabetes (T2D) who have multiple CV risk factors (59.4% had at least one RF of dyslipidemia, HBP or smoking) or established CV disease (40.6% had ASCVD upon entry).
  - Mean A1c 8.3% +/- 1.2%, mean age 63.8 years +/- 6.8 yrs; duration of diabetes 11.8 +/- 7.8 yrs, 62.6% male and body mass index 32.1 ± 6.0 kg/m²
  - Diabetes Obes Metab. 2018 May;20(5):1102-1110
DECLARE-TIMI-58 Trial

• September 24, 2018 Astra Zeneca announced that dapagliflozin, Farxiga met its primary safety endpoint of non-inferiority for major adverse cardiovascular events (MACE). Dapagliflozin achieved a statistically-significant reduction in the composite endpoint of hospitalization for heart failure (hHF) or CV death, one of the two primary efficacy endpoints. Additionally, fewer MACE events were observed with dapagliflozin for the other primary efficacy endpoint, however, this did not reach statistical significance.
• Detailed trial results will be presented on 10 November, 2018 at the American Heart Association Scientific Sessions in Chicago.

Concerns with SGLT-2 Inhibitors?

• I would not routinely recommend an SGLT-2 inhibitor in the following patients:
  – Patients with impaired renal function (eGFR of < 45 ml/min maybe less than 60?).
  – Patients with diabetic neuropathy, previous foot ulcers, previous amputations and/or peripheral vascular disease.
  – Patients at risk for falls or with orthostatic hypotension.
  – Patients with a history of osteoporosis, osteopenia, decreased BMD or history of fractures.

SGLT-2 Inhibitors and Necrotizing Fasciitis of the Perineum MedWatch 8-29-2018

• FDA is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier’s gangrene. We are requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient Medication Guide.
• In the five years from March 2013 to May 2018, the FDA identified 12 cases (7 men and 5 women) of Fournier’s gangrene in patients taking an SGLT2 inhibitor. This number includes only reports submitted to FDA and found in the medical literature.

SGLT-2 Inhibitors and Necrotizing Fasciitis of the Perineum MedWatch 8-29-2018

• All 12 patients were hospitalized and required surgery and on patient died.
• Looking at all drugs for diabetes over 34 years the FDA was only able to identify a total of 6 previous cases, all in men.
• Patient Information: Seek medical attention immediately if you experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4 F or a general feeling of being unwell. These symptoms can worsen quickly.
FDA Safety Announcement

• [5-15-2015] The FDA is warning that the SGLT-2 inhibitors: canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization.
• Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness.

SGLT-2 Inhibitors and DKA

• A new analysis from Wake Forest, UNC and Duke) found 39 cases of DKA among 11,197 people with prescriptions for SGLT2 inhibitors (74% in patients with Type 2 DM/ 82% C; 15% D and 3% E). Of these, 26 patients had glucose ≤300 mg/dL, with a mean glucose of 266 mg/dL. Symptoms reported included nausea and vomiting (49%), although researchers said “it is unclear if that was a cause, contributor, or consequence of the DKA.” Also, 67% of the patients had some other obvious event such as surgery, an insulin dose reduction, or weight loss.
• The authors recommend “a high index of suspicion for DKA in patients taking SGLT2 inhibitors with unexplained malaise or gastrointestinal symptoms and recommend measuring urine or plasma ketones in that setting.”

Ertugliflozin – Steglatro by Merck and Pfizer

• Dec. 20, 2017 the FDA approved ertugliflozin – Steglatro a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
• Dosage: Recommended starting dose is 5 mg once daily, taken in the morning, with or without food. Increase dose to 15 mg once daily in those tolerating ertugliflozin and needing additional glycemic control.
  – Elimination T1/2 is ~ 16.5 hours
  – Initiation or continued use is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m2.

Ertugliflozin – Steglatro

• Lower Limb Amputation: Across seven Phase 3 clinical trials in which ertugliflozin was studied as monotherapy and in combination with other antihyperglycemic agents, non-traumatic lower limb amputations occurred in 1 of 1,450 (0.1%) in the non-ertugliflozin group, 3 of 1,716 (0.2%) in the ertugliflozin 5 mg group, and 8 of 1,693 (0.5%) in the ertugliflozin 15 mg group.
  – consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers.

Cost: Merck has established a list price (Wholesale Acquisition Cost) of $8.94 per day for STEGLATRO (about 40% less than other SGLT-2’s)
• Steglumet (ertugliflozin plus metformin) BID WAC ~$8.94/day
  – 2.5 mg plus 500 mg
  – 2.5 mg plus 1000 mg
  – 7.5 mg plus 500 mg
  – 7.5 mg plus 1000 mg
• Steglujan (ertugliflozin plus sitagliptin) QD WAC ~ $17.45/day
  – 5 mg plus 100 mg
  – 15 mg plus 100 mg
Ertugliflozin – Steglatro

- The CVOT Trial VERTIS CV Study (MK-8835-004) has enrolled 8,000 patients with evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems. Randomized to 5 mg or 15 mg of ertugliflozin or placebo and followed for up to 6 plus years, anticipated completion fall of 2019.
- Primary Outcome: Time to First Occurrence of MACE (Composite Endpoint of Major Adverse Cardiovascular Events [Cardiovascular Death, Non-fatal Myocardial Infarction or Non-fatal Stroke])

Liraglutide – Victoza by Novo-Nordisk

- A human analog of the glucagon-like peptide-1 (GLP-1) with 97% amino acid sequence homology to endogenous human GLP-1.
  - T1/2 ~11-15 hrs
  - 1.2 mg dose (2 pens/mo)
    - $497.00 GoodRx.com
  - 1.8 mg dose (3 pens/mo)
    - $743.00 GoodRx.com
- Adjunct to diet and exercise for Type 2 DM but not first line and no data in combo with prandial insulin

LEADER CV Safety Trial with Liraglutide

- 9340 patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
  - The median follow-up was 3.8 years.
- The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (HR 0.87; 95% CI, 0.78 to 0.97; P<0.001 for noninferiority; P = 0.01 for superiority) ARR 1.9%, NNT=53
- The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (HR 0.85; 95% CI, 0.74 to 0.97; P = 0.02). ARR 1.4%, NNT=72
- The rates of nonfatal myocardial infarction (HR 0.88), nonfatal stroke (HR 0.89), and hospitalization for heart failure (HR 0.87) were all nonsignificantly lower in the liraglutide group than in the placebo group.

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LEADER CV Safety Trial with Liraglutide

- Microvascular Outcomes: The incidence of a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (HR 0.84; 95% CI, 0.73 to 0.97; P = 0.02)
  - The difference was driven by a lower rate of nephropathy events in the liraglutide group (1.5 vs. 1.9 events per 100 patient-years of observation; HR 0.78; 95% CI, 0.67 to 0.92; P = 0.003)
  - The incidence of retinopathy events was nonsignificantly higher in the liraglutide group than in the placebo group (0.6 vs. 0.5 events per 100 patient-years; HR 1.15; 95% CI, 0.87 to 1.52; P = 0.33).

LEADER CV Safety Trial with Liraglutide

- The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group (18 vs. 23) than in the placebo group.
  - Pancreatic carcinoma 13 (0.3) with liraglutide vs. 5 (0.1) with placebo p=0.06
  - Medullary thyroid carcinoma 0 with liraglutide vs. 1 (<0.1) with placebo p=0.32

ELIXA – a cardiovascular safety outcomes trial of lixisenatide

- Lixisenatide (Adlyxin) was FDA approved 7/28/2016
- March 2015, Sanofi announced top-line results of the ELIXA outcome study, a Phase IIIb cardiovascular safety outcomes trial of lixisenatide (Adlyxin®) compared to placebo in 6,000 a high-risk (post ACS) population of adults with Type 2 diabetes for the evaluation of cardiovascular safety.
  - First CV safety trial for any of the GLP-1 Agonists to report out.
  - The results from the study showed that lixisenatide was non-inferior, although not superior, to placebo for cardiovascular safety, and establish that there is no additional cardiovascular risk, in a high-risk patient, associated with treatment with lixisenatide, helping to support the existing consensus around the therapeutic benefits of lixisenatide.
    - Results presented at ADA in Boston on June 9, 2015

EXSCEL Trial: Bydureon CV Safety Trial

- EXSCEL is a Phase IIIb/IV, double-blind, placebo-controlled, global CV outcomes trial conducted in 35 countries and enrolled more than 14,000 patients with type-2 diabetes or without additional CV risk factors or prior CV events. Participants were randomized to receive exenatide once-weekly 2mg or matching placebo by subcutaneous injections. Primary composite CV endpoint risk of MACE, a composite endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke.
  - EXSCEL was run jointly by two academic research organizations - the Duke Clinical Research Institute (Durham, NC, US) and the University of Oxford Diabetes Trials Unit (Oxford, UK)
  - AstraZeneca Press Release May 23, 2017
EXSCEL Trial: Bydureon CV Safety Trial

• The EXSCEL trial met its primary safety objective of non-inferiority for MACE. These results address the US Food and Drug Administration (FDA) requirement that medicines to treat T2D are not associated with an increase in CV risk. Fewer CV events were observed in the Bydureon arm of the trial, however, the efficacy objective of a superior reduction in MACE did not reach statistical significance.

– A full evaluation of the EXSCEL data is ongoing. The results will be presented at the European Association for the Study of Diabetes (EASD) annual meeting on Thursday, 14 September 2017 in Lisbon, Portugal.

Semaglutide - Ozempic a once a week GLP-1 analog by Novo Nordisk

• Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
• Available as a carton of 1 Pen (NDC 0169-4132-12) Pen delivers doses of 0.25 mg or 0.5 mg per injection 6 Novofine® Plus needles Intended for treatment initiation at the 0.25 mg dose and maintenance treatment at the 0.5 mg dose
• Carton of 2 Pens (NDC 0169-4136-02) Pen delivers doses of 1 mg per injection 4 Novofine® Plus needles Intended for maintenance treatment at the 1 mg dose only
• SC solution single-patient-use pen 1.34mg/mL; delivers doses of 0.25mg, 0.5mg, or 1mg.

The company has announced that the drug will cost $700.00 per box of 2 pens, which it described as “at parity” with drugs in the same class.

Semaglutide - Ozempic

Starting and maintenance dose
Pen delivers doses of 0.25 mg and 0.5 mg

Maximum maintenance dose
Pen delivers dose of 1 mg

Semaglutide CV Data – SUSTAIN 6 Trial

• Sustain 6 randomly assigned 3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly (GLP-1 agonist) semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks.
• The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.
  – At baseline, 2735 of the patients (83.0%) had established cardiovascular disease, chronic kidney disease, or both.
  – Mean duration of diabetes was 13.9 years and mean HbA1c was 8.7%. 93.5% were taking antihypertensive medication, 76.5% were receiving lipid-lowering drugs, and 76.3% were receiving antithrombotic medications.
  – Drug is investigational and not yet filed with the FDA
  – NEJM on-line 9-16-2016

Semaglutide CV Data – SUSTAIN 6 Trial

• The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P=0.001 for noninferiority). NNT 45
• Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P=0.12); nonfatal stroke occurred in 1.6% and 2.7%, respectively (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P=0.04).
• Rates of death from cardiovascular causes were similar in the two groups.
  – NEJM on-line 9-16-2016
Sustained CV Benefit – SUSTAIN 6 Trial

- From an overall baseline of 8.7%, semaglutide significantly reduced HbA1c by 1.4% and 1.1% (for the two doses) vs 0.4% for placebo.
- Body weight “decreased by almost 5 kg with the 1.0-mg dose of semaglutide, from a mean of 92.1 kg,” compared with weight loss of 3.6 kg, on average, in the 0.5-mg group and 0.5 to 0.7 kg in the placebo recipients.
  - Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02).
  - This trend was also seen in the LEADER Trial with lixisenatide and in the DCCT with rapid lowering of BG with insulin.

Sustained CV Benefit – SUSTAIN 7 Trial

- 68% of people treated with 0.5 mg semaglutide compared with 52% of people treated with 0.75 mg dulaglutide reached the ADA treatment goal A1c of <7.0%, and 79% of people treated with 1.0 mg semaglutide compared to 67% with 1.5 mg dulaglutide reached the treatment goal.
- From a mean baseline body weight of 95 kg and a BMI of 33.5 kg/m², people treated with 0.5 mg semaglutide experienced a statistically significant and superior weight loss of 4.6 kg compared to 2.3 kg with 0.75 mg dulaglutide. People treated with 1.0 mg semaglutide experienced a statistically significant and superior weight loss of 6.5 kg compared to 3.0 kg with 1.5 mg dulaglutide.
- Adverse effects mainly GI (nausea) were similar.

Investigational Oral Semaglutide

- Once-daily tablet formulated with SNAC
  - SNAC (Sodium N-(6-hydroxybenzoyl) amino) caprylate
    - Carrier molecule that enhances absorption
    - Forms weak noncovalent bonds with oral semaglutide
    - Local buffering effect: Prevents breakdown by gastric enzymes and stomach acid
    - Locally absorbed in the stomach near the site of tablet erosion
  - Given that the Sustain-6 outcomes trial was relatively brief (~2 years), with fewer patients (~3300) than a trial designed to prove CV benefits, Novo did not ask the FDA for a CV risk-reduction claim for semaglutide and the FDA did not approve a CV label claim.
  - The company does plan a more extensive follow-up study beginning next year to assess those benefits, just as it did with Victoza, which now has an FDA approval as a CV risk-reduction tool.

Investigational Oral Semaglutide

- 22-2-2018 PIONEER 1 was a 26-week, randomized, double-blinded, placebo-controlled, four-armed, parallel-group, multinational trial comparing the efficacy and safety of three dose levels of once-daily oral semaglutide vs placebo in people with type 2 diabetes treated with diet and exercise only. 703 people were enrolled in PIONEER 1 and randomized 1:1:1:1 to receive either a dose of oral semaglutide (5, 7 or 14 mg) or placebo once daily. The primary endpoint was change in HbA1c from baseline at week 26.
  - Patients treated with 3, 7 and 14 mg oral semaglutide achieved reductions in HbA1c of 0.8%, 1.3% and 1.5%, respectively, compared to a reduction of 0.1% in people treated with placebo from a mean baseline of 8.0%.
  - Patients treated with 3, 7 and 14 mg oral semaglutide experienced a weight loss of 1.7 kg, 2.5 kg and 4.1 kg, respectively, compared to a weight loss of 1.5 kg in people treated with placebo. (mean baseline body weight of 88 kg and a BMI of 31.8 kg/m²)
    - The most common adverse event for all three oral semaglutide doses was mild to moderate nausea (5-16% vs. 6% placebo), which diminished over time.
**Dulaglutide – Trulicity**

- FDA required Rewind CV safety trial ~9600 patients 50 and older with Type 2 diabetes with CV disease or older patients with 2 or more CV risk factors treated for up to 6.5 years. The Rewind Trial is expected to be completed July 2018.

**REDUCE-IT Trial with Icosapent ethyl (EPA) - Vacepa**

- September 2018, Amarin/Kowa announced the topline results of the REDUCE-IT Trial a cardiovascular (CV) outcomes study of VASCEPA (icosapent ethyl) capsules met its pre-specified primary composite endpoint (4 point MACE of CV death, nonfatal myocardial infarction (MI, including silent MI), nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalization) in the intent-to-treat population:  
  - Randomized 8,179 patients on a 1:1 basis to statin plus VASCEPA 4g/day or statin plus placebo and compared the incidence of MACE between treatment arms over a median period of 4.9 years.  
  - Baseline LDL-C controlled to between 41-100 mg/dL (median baseline 75 mg/dL) by statin therapy and with various cardiovascular risk factors including elevated triglycerides between 150-499 mg/dL (median baseline 216 mg/dL) and either established cardiovascular disease (secondary prevention) or diabetes mellitus and at least one other CV risk factor (primary prevention).  
  - Showed reduction in a composite of major adverse cardiovascular events (MACE) of approximately 25% — P value <0.001 (highly statistically significant).  
  - Additional updates on REDUCE-IT study results are planned in a peer-reviewed publication and presentation of REDUCE-IT results will occur at the late-broader session at the 2018 Scientific Sessions of the American Heart Association (AHA) on November 10, 2018 in Chicago.

**Epinephrine Inj 0.3 mg - Symjepi**

  - Initially only available as a single-dose prefilled 0.3 mg/0.3 mL syringe for patients weighing 66 lbs or more. (A 0.15 mg dose is pending FDA approval)  
  - Symppr differs from EpiPen in that it’s a manual injection (not an auto-injector pen). You’ll inject the medication either intramuscularly (into the muscle) or subcutaneously (under the skin) into the outer thigh area. Symjepi can be injected through clothing if necessary.  
  - In studies Symjepi was shown to be easier to use, smaller in size, easier to carry and preferred over Mylan’s EpiPen.  
  - 7/1/18 Adams has found a partner Novartis/Sandoz to market the drug in the US. Sandoz will obtain the United States commercial rights to Symjepi in exchange for an upfront fee and potential performance-based milestone payments. Additionally, Adams and Sandow will equally share net profits.  
  - Adams has also filed an IND for naloxone using the same delivery system.

**FDA - Approved Indication and Limitations of Use for VASCEPA**

- VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (>500 mg/dL) hypertriglyceridemia.  
  - In patients with severe hypertriglyceridemia, the effect of VASCEPA on cardiovascular mortality or morbidity or on the risk of pancreatitis has not been determined.  
  - The daily dose of VASCEPA is 4 grams per day taken as four 0.5-gram capsules or two 1-gram capsules twice daily with food.  
  - Cost 1 Gm caps x 120 ~ $242.00, 500 mg caps x 240 ~$282.00

GoodRx.com 9/26/18
**Epinephrine Inj 0.3 mg - Symjepi**

1. Ready to Use SYMJEPI
2. Insert needle into subcutaneous tissue
3. Get Help
4. After Use

**Migraine Headache**

- Migraine has a global prevalence of 15 to 18% and is a leading cause of disability worldwide.
- Chronic migraine (CM), occurring in approximately 2% of the population, has been defined as the occurrence of at least 15 days with headache per month for at least 3 months.
- Episodic migraine (EM), has been defined as 0 to 14 days with headache per month.
- The relationship between EM and CM is complex. EM progresses to CM at the rate of 2.5% per year, and CM often remits to EM (2-year transition rate of 26%).

**Erenumab-aooe – Aimovig by Amgen and Novartis**

- May 17, 2018 The U.S. Food and Drug Administration approved Aimovig (erenumab-aooe) for the preventive treatment of migraine in adults. The treatment is given by once-monthly self-injections. Aimovig is the first FDA-approved preventive migraine treatment in a new class of drugs that work by blocking the activity of calcitonin gene-related peptide, a molecule that is involved in migraine attacks.
- Erenumab is a human immunoglobulin G2 (IgG2) monoclonal antibody. Erenumab is specific and selective to CGRP receptors, exerting action by full competitive inhibition of the receptor.

**Erenumab-aooe – Aimovig**

- Pharmacokinetics: Median time to peak concentration after subcutaneous administration of erenumab 1 mg to 210 mg ranged from 4 to 11 days (mean ~ 6 days).
- The estimated elimination half-life of erenumab in a typical 70 kg person receiving erenumab 70 mg subcutaneously is approximately 21 days.
- Erenumab-aooe is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

**Erenumab-aooe – Aimovig**

- Calcitonin gene-related peptide (CGRP) is a peptide expressed in the peripheral and central nervous systems. At nerve endings located on cerebral vascular smooth muscle, CGRP is a potent proinflammatory peptide that is released from the trigeminal ganglia neurons, resulting in vasodilation of the cranial vasculature. CGRP receptors are found in the vasculature, trigeminal sensory afferents, trigeminal ganglion, and trigeminal nucleus caudalis. CGRP modulates vascular nociception and also acts as a neurotransmitter in the trigeminal ganglion and second-order neurons in the trigeminal nucleus caudalis to facilitate nociceptive transmission.

**Erenumab-aooe – Aimovig**

- Elevated blood and salivary CGRP levels occur in patients with migraines, cluster headaches, facial pain disorders, trigeminal neuralgia, chronic paroxysmal hemicrania, trigeminal neuralgia, and rhinosinusitis. Levels are elevated during a migraine attack and between migraine attacks in patients with chronic migraines. In studies to determine the role of elevated CGRP levels in patients with migraine headaches (ie, causative or secondary to migraine), exogenous CGRP infusions were shown to trigger migraine attacks. In addition, elevated CGRP levels predict patient response to treatment with triptans and dihydroergotamine mesylate in those with acute migraine attacks, and to on a botulinumtoxin A in those with chronic migraines. Monoclonal antibody therapies targeting the CGRP receptor have shown efficacy in episodic and chronic migraine prevention.
Erenumab-aooe – Aimovig

The effectiveness of erenumab for the preventive treatment of migraine was evaluated in three clinical trials.

- First trial included 955 patients with a history of episodic migraines (with or without aura) for at least 12 months according to International Headache Society criteria (i.e., 4 to 15 migraine days per month on average across the 3 months prior to screening and during baseline). Baseline mean number of monthly migraine days (MMDs) was 8.3.
- Patients were randomized 1:1:1 to receive subcutaneous injections of erenumab 70 mg, erenumab 140 mg, or placebo once a month for 6 months. If the patient was using only 1 prophylactic medication at baseline and the dose was stable for at least 2 months prior to the start of the baseline phase, it could be continued throughout the study.
- Patients were randomized 1:1:1 to receive subcutaneous injections of erenumab 70 mg, erenumab 140 mg, or placebo once a month for 3 months. If the patient was using only 1 prophylactic medication at baseline and the dose was stable for at least 2 months prior to the start of the baseline phase, it could be continued throughout the study.

- The mean migraine frequency at baseline was approximately 18 migraine days per month and was similar across treatment groups.
- The study excluded patients with medication overuse headache caused by quinine overuse and patients with concurrent use of migraine preventive treatments. Patients with myocardial infarction, stroke, transient ischemic attacks, unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months prior to screening were also excluded.

Erenumab-aooe – Aimovig

- Study 3 (NCT 02066415) was a randomized, multi-center, 3-month, placebo-controlled, double-blind study evaluating erenumab as a preventive treatment of chronic migraine. A total of 667 patients with a history of chronic migraine with or without aura were randomized to receive erenumab 70 mg (N = 191), erenumab 140 mg (N = 190), or placebo (N = 286) by subcutaneous injections once monthly for 3 months. Patients were allowed to use acute headache treatments including migraine-specific medications (i.e., triptans, ergotamine derivatives) and NSAIDs during the study. The mean migraine frequency at baseline was approximately 18 migraine days per month and was similar across treatment groups.
- The study excluded patients with medication overuse headache caused by quinine overuse and patients with concurrent use of migraine preventive treatments. Patients with myocardial infarction, stroke, transient ischemic attacks, unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months prior to screening were also excluded.

Erenumab-aooe – Aimovig

- The second trial ARISE included 577 adults with a history of episodic migraines and high migraine frequency. Baseline mean number of MMDs was 8.3.
- Exclusion criteria included age older than 50 years at migraine onset; history of cluster headaches or hemiplegic migraine headaches; inability to differentiate migraines from other headaches; no therapeutic response with more than 2 categories for prophylactic treatment of migraine after an adequate therapeutic trial; concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase; use of butalbital tonics; active chronic pain syndromes (e.g., fibromyalgia, chronic pelvic pain); history of major psychiatric disorder or seizure disorder or other significant neurological conditions other than migraine; history of HIV infection; or CEO 12 months prior to screening.
- Intervention: Patients were randomized 1:1:1 to receive subcutaneous injections of erenumab 70 mg, erenumab 140 mg, or placebo once a month for 3 months.

Erenumab-aooe – Aimovig

- **Primary End Point:** Mean reduction in MMD from baseline was –3.2 days with erenumab 70 mg (P=0.001 vs placebo), –3.7 days with erenumab 140 mg (P=0.001 vs placebo), and –1.8 days with placebo during weeks 13 to 24. ~ 1 to 2 days reduction per month.

- **Secondary End Point(s):** Reduction in MMD of 50% or more was achieved by 43%, 50%, and 27% of patients in the erenumab 70 mg, erenumab 140 mg, and placebo groups, respectively (P=0.001 for both erenumab groups vs placebo).

- **Exploratory patient-reported outcome values showed improvements from baseline in quality of life, disability, and migraine-related impact on life.**

- **Erenumab adverse reactions and tolerability were similar to placebo.**

Erenumab-aooe – Aimovig

- **Secondary End Point(s): Reduction in MMD of 50% or more was achieved by 40% and 30% of patients in the erenumab and placebo groups, respectively (odds ratio, 1.6; P=0.01); number needed to treat was 10.**

- **Mean reduction in MMD from baseline was −2.9 days with erenumab compared to −1.8 days in the placebo arm (P<0.001) during weeks 9 to 12.**

- **Monthly acute migraine rescue medication use was reduced by a mean of −1.2 days in the erenumab group and −0.6 days in the placebo group (P=0.002).**

- **Exploratory patient-reported outcome values showed improvements in quality of life, disability, and migraine-related impact on life.**

- **The safety profile of erenumab was similar to placebo.**

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**Table 5: Efficacy Endpoints at Month 3 in Study 3**

<table>
<thead>
<tr>
<th></th>
<th>Erenumab 70 mg (N = 188)</th>
<th>Erenumab 140 mg (N = 187)</th>
<th>Placebo (N = 281)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Migraine Days (MMD)</strong></td>
<td>-2.9 (P &lt; 0.001)</td>
<td>-2.4 (P &lt; 0.001)</td>
<td>-1.2</td>
</tr>
<tr>
<td><strong>Daily migraine use</strong></td>
<td>-1.1 (P &lt; 0.001)</td>
<td>-1.2 (P = 0.01)</td>
<td>-1.1</td>
</tr>
<tr>
<td><strong>Adjusted P-value</strong></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

The Lancet Neurology Volume 16, Issue 6, June 2017, Pages 425-434
Erenumab—aooe—Aimovig

The safety of erenumab has been evaluated in 2,537 patients with migraine who received at least one dose of erenumab, representing 2,210 patient-years of exposure. Of these, 2,257 patients were exposed to 70 mg or 140 mg once monthly for at least 6 months, 1,186 patients were exposed for at least 12 months, and 267 patients were exposed for at least 18 months.

Table 1: Adverse Reactions Occurring with an Incidence of at Least 2% for Either Dose of AIMOVIG and at Least 2% Greater Than Placebo During the First 3 Months in Studies 1, 2, and 3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>70 mg Once Monthly</th>
<th>140 mg Once Monthly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reaction*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Overall: nausea or vomiting</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*The reactions include multiple adverse events related terms, such as nausea, vomiting, and retching. In patients receiving erenumab 70 mg once monthly, 20.5% (48/236) of subjects developed anti–erenumab aooe antibodies (as assessed by ELISA); of these, 30.4% (15/49) developed neutralizing antibody activity. In patients receiving erenumab 140 mg once monthly, 11.1% (5/45) of subjects developed anti–erenumab aooe antibodies (as assessed by ELISA); of these, 11.1% (1/9) developed neutralizing antibody activity. Although these data do not demonstrate an impact of anti–erenumab aooe antibody development on the efficacy or safety of erenumab in these patients, the available data are too limited to make definitive conclusions.

Erenumab—aooe—Aimovig

- The recommended dosage of Erenumab is 70 mg injected subcutaneously once monthly. Some patients may benefit from a dosage of 140 mg injected subcutaneously once monthly, which is administered as two consecutive subcutaneous injections of 70 mg each.
- Administer in the abdomen, thigh, or upper arm subcutaneously.
- Erenumab comes in 2 different types of devices: a single-dose (1 time) prefilled autoinjector or a single-dose (1 time) prefilled syringe. Estimated cost ~$7,000.00/year

Erenumab—aooe—Aimovig

- In a 1-year open-label extension study in 451 patients with chronic migraine, patients taking 140 mg and 70 mg of erenumab experienced reductions of average monthly migraine days of 10.5 days and 8.5 days, respectively, compared to a baseline of 18.1 days. Patients treated with Aimovig experienced reductions in monthly migraine days of:
  - 50 percent or more: 67 percent on 140 mg and 53 percent on 70 mg
  - 75 percent or more: 42 percent on 140 mg and 27 percent on 70 mg
  - 100 percent reduction: 13 percent on 140 mg and 6 percent on 70 mg
  -- Amgen press release 6/28/2018

Pending FDA Approval for the Prevention of Migraines

- Several pharmaceutical companies now have monoclonal antibody drugs in the pipeline and are competing to get their products on the shelves first. Collaborators Novartis and Amgen were first to FDA approval with erenumab in May 2018. Hot on their heels are Israeli pharmaceuticals firm Teva with fremanezumab (SC monthly or quarterly NEJM 2017;377:2113-22), and Eli Lilly with galcanezumab (SC monthly JAMA Neurol. doi:10.1001/jamaneurol.2018.1212 Published online May 29, 2018). These monoclonal antibodies are directed against CGRP and not the receptor. Both firms aim to have FDA approval in late 2018.
- Oral versions of a CGRP inhibitor (receptor antagonists) are being developed by Allergen (ubrogepant 25 and 50 mg in the ACHIEVE I and II Phase III studies) and Merck/Allergan (atogepant).
Potential for CGRP-mAbs in patients with episodic and chronic migraine?

- An appreciable proportion of patients in the clinical studies achieved ≥ 75% reduction in migraine days during their treatment with the CGRP-pathway-targeted mAbs. If reliable clinical or biologic markers of “super-responders” were identified, then perhaps the concept of personalized migraine prevention based on mechanism could be realized?

- Ongoing clinical studies, postmarketing surveillance, and clinical practice data will be needed for evidence of the long-term efficacy and safety of the new migraine preventive therapies, and of their effectiveness in different patient groups.

Fremanezumab-vfrm – Ajovy by Teva

- 9/14/18 FDA approved Fremanezumab-vfrm for the prevention of migraines in adults.

- A fully humanized IgG2a/κkappa monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand that binds to the CGRP ligand and blocks its binding to the receptor. Fremanezumab-vfrm is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

- Recommended Dosage: Two subcutaneous dosing options of Ajovy are available to administer the recommended dosage:
  - 225 mg monthly, (available in 225 mg/1.5 mL single-dose prefilled syringe) or
  - 675 mg every 3 months (quarterly), which is administered as three consecutive subcutaneous injections of 225 mg each. Cost ~$400.00/prefilled syringe

Fremanezumab-vfrm – Ajovy

- Remove fremanezumab-vfrm/AJOVY from the refrigerator. Prior to use, allow the medication to sit at room temperature for 30 minutes protected from direct sunlight. Do not warm by using a heat source such as hot water or a microwave. Do not use if it has been at room temperature for 24 hours or longer.

Fremanezumab-vfrm – Ajovy

- Study 1 (NCT 02629861) included adults with a history of episodic migraine (patients with <15 headache days per month). All patients were randomized (1:1:1) to receive subcutaneous injections of either fremanezumab 675 mg every three months (quarterly), fremanezumab 225 mg monthly, or placebo monthly, over a 3-month treatment period. Patients were allowed to use acute headache treatments during the study. A subset of patients (21%) was allowed to use one additional concomitant preventive medication.

- 875 patients (742 females, 133 males), ranging in age from 18 to 70 years, were randomized. A total of 791 patients completed the 3-month double-blind phase. The mean migraine frequency at baseline was approximately 9 migraine days per month, and was similar across treatment groups.
Fremanezumab-vfrm – Ajovy

- Study 2 (NCT 02621931) included adults with a history of chronic migraine (patients with ≥15 headache days per month). All patients were randomized (1:1:1) to receive subcutaneous injections of either fremanezumab 675 mg starting dose followed by 225 mg monthly, 675 mg every 3 months (quarterly), or placebo monthly, over a 3-month treatment period. Patients were allowed to use acute headache treatments during the study. A subset of patients (21%) was allowed to use one additional concomitant, preventive medication.

- 1130 patients (991 females, 139 males), ranging in age from 18 to 70 years, were randomized. A total of 1034 patients completed the 3-month double-blind phase.

Fremanezumab-vfrm – Ajovy

- In 3-month placebo-controlled studies, treatment-emergent ADA responses were observed in 6 out of 1701 (0.4%) fremanezumab–treated patients. One of the 6 patients developed anti-fremanezumab neutralizing antibodies at Day 84. In the ongoing long-term open-label study, ADA were detected in 1.6% of patients (30 out of 1888). Out of 30 ADA-positive patients, 17 had a neutralizing activity in their post-dose samples. Although these data do not demonstrate an impact of anti-fremanezumab-vfrm antibody development on the efficacy or safety of fremanezumab in these patients, the available data are too limited to make definitive conclusions.

Fremanezumab-vfrm – Ajovy

- The most common adverse reactions were at the injection site (eg, injection-site pain, injection-site erythema), and occurred in 47% of the group receiving fremanezumab quarterly, 47% of those receiving fremanezumab monthly, and 40% of the placebo group.

- Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with fremanezumab in clinical trials. Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month after administration.

Galcanezumab-gnlm – Emgality by Lilly

- 9/27/18 FDA approved galcanezumab-gnlm for the prevention of migraines in adults. A humanized IgG4 monoclonal antibody specific for calcitonin-gene related peptide (CGRP) ligand and blocks its binding to the receptor.

Galcanezumab-gnlm – Emgality

Pharmacokinetics:

- The time to maximum concentration is 5 days, and the elimination half-life is 27 days.

- Galcanezumab-gnlm is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

- The pharmacokinetics of galcanezumab-gnlm were not affected by age, sex, race, or subtypes of migraine spectrum (episodic or chronic migraine), based on a population pharmacokinetics analysis. Body weight has no clinically relevant effect on the pharmacokinetics of galcanezumab-gnlm.

- Renal and hepatic impairment are not expected to affect the pharmacokinetics of galcanezumab-gnlm.

- Galcanezumab-gnlm is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.
Galcanezumab-gnlm – Emgality

- Episodic Migraine: EVOLVE-1 (Study 1; North America) and EVOLVE-2 (Study 2; Global) were 6-month, randomized, multicenter, double-blind, placebo-controlled trials in patients with episodic migraine (4-14 migraine days/month).
- Patients were randomized in a 1:1:2 ratio to receive once-monthly subcutaneous injections of Galcanezumab 120 mg, Galcanezumab 240 mg, or placebo. All patients in the 120 mg group received an initial 240 mg loading dose. (Note-only the 120 mg dose after a loading dose of 240 mg is FDA approved)
- Patients were allowed to use acute headache treatments, including migraine-specific medications (i.e., triptans, ergotamine derivatives during the study).

Galcanezumab-gnlm – Emgality

- Chronic Migraine: REGAIN Study 3 (NCT02614261) included adults with a history of chronic migraine (≥15 headache days per month with ≥8 migraine days per month). All patients were randomized in a 1:1:2 ratio to receive once-monthly subcutaneous injections of Galcanezumab 120 mg, Galcanezumab 240 mg, or placebo over a 3-month treatment period. All patients in the 120 mg group received an initial 240 mg loading dose. (Note-only the 120 mg dose after a loading dose of 240 mg is FDA approved)

Galcanezumab-gnlm – Emgality

- Adverse Effects: Injection site reactions (18% galcanezumab vs. 13% placebo) include multiple related adverse event terms, such as injection site pain, injection site reaction, injection site erythema, and injection site pruritus.
- Immunogenicity: With 12 months of treatment in an open-label study, up to 12.5% (16/128) of Emgality-treated patients developed anti-galcanezumab-gnlm antibodies, most of whom tested positive for neutralizing antibodies.
- Although anti-galcanezumab-gnlm antibody development was not found to affect the pharmacokinetics, safety, or efficacy of Emgality in these patients, the available data are too limited to make definitive conclusions.

Low Dose Aspirin Dosage for CV Risk Reduction?

- Low-dose aspirin may not be effective in preventing cardiovascular events in people weighing 70 kg (154 pounds) or more, a Lancet study suggests.
- Researchers analyzed 10 trials that evaluated aspirin versus controls for primary prevention of cardiovascular events in 120,000 people.
- Daily, low-dose aspirin (75–100 mg) was associated with reduced risk for cardiovascular events among those weighing less than 70 kg (odds ratio, 0.77), but there was no significant effect for heavier patients — roughly 80% of men in the study and nearly half of women weighed 70 kg or more. In the heavier group, low-dose aspirin may be even less effective in smokers and in those who take enteric-coated aspirin.

- Lancet Published Online July 12, 2018 http://dx.doi.org/10.1016/ S0140-6736(18)31133-4
Low Dose Aspirin Dosage for CV Risk Reduction?

- High-dose aspirin (300–325 or 500 mg), meanwhile, appeared to be effective in reducing primary cardiovascular events only patients weighing 70 kg or more (OR, 0.79).
- Commentators said that people with more body mass may have more esterases, which clear aspirin and would reduce the bioavailability of the drug.

The authors conclude: "A one-dose-fits-all approach to aspirin is unlikely to be optimal, and a more tailored strategy is required."

ASCEND (A Study of Cardiovascular Events in Diabetes)

- A randomized 2x2 factorial design study of aspirin 100 mg EC versus placebo, and of omega-3 fatty acid supplementation 1 gram versus placebo, for the primary prevention of cardiovascular events in people with diabetes.
- Randomly assigned 15,480 adults (mean age 63 +/- 9.2 yrs, 63% male, 96.5% white, 94% Type 2 DM) who had diabetes but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo and omega 3 FA 1 Gm daily or olive oil placebo.

ASCEND Trial

- During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%, respectively) or all cancers (897 [11.6%] and 887 [11.5%]); long-term follow-up for these outcomes is planned.

ASCEND Trial – Omega 3 FA

- Patients were given 840 mg of marine n–3 fatty acids (460 mg of eicosapentaenoic acid [EPA] and 380 mg of docosahexaenoic acid [DHA]) (fatty acid group) or a matching placebo capsule (olive oil) to be taken once daily.

ASCEND Trial - Aspirin

- During a mean follow-up of 7.4 years (adherence rate, 76%), a serious vascular event occurred in 689 patients (9.8%) in the fatty acid group and in 732 (9.2%) in the placebo group (rate ratio, 0.97; 95% confidence interval [CI], 0.87 to 1.08; P=0.55). The composite outcome of a serious vascular event or revascularization occurred in 882 patients (11.4%) and 887 patients (11.5%), respectively (rate ratio, 1.00; 95% CI, 0.91 to 1.09). Death from any cause occurred in 752 patients (9.7%) in the fatty acid group and in 788 (10.2%) in the placebo group (rate ratio, 0.95; 95% CI, 0.86 to 1.05). There were no significant between-group differences in the rates of nonfatal serious adverse events.

ASCEND Trial – Omega 3 FA

- During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%, respectively) or all cancers (897 [11.6%] and 887 [11.5%]); long-term follow-up for these outcomes is planned.

Cannabidiol Oral Solution (CBD-OS) – Epidiolex C-V by GW Research Labs

- The IND for CBD-OS was submitted in 2014, and it was granted Orphan Drug Status and a Rare Pediatric Designation for the treatment of Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) and Fast-Track Designation for DS.
- FDA approved 6/25/2018 but the DEA has 90 days to determine what Schedule the medication will be.
- Schedule V by the DEA (9/27/2018) - Schedule V drugs are said to represent little potential for abuse.
- The efficacy of CBD-OS was assessed in 3 Phase 3 Clinical Trials: 2 in LGS (study 1414 and 1423) and 1 in DS (Study 1332B).
Lennox-Gastaut syndrome and Dravet syndrome

- Lennox-Gastaut syndrome begins in childhood. It is characterized by multiple types of seizures. People with Lennox-Gastaut syndrome begin having frequent seizures in early childhood, usually between ages 3 and 5. More than three-quarters of affected individuals have tonic seizures, which cause the muscles to contract uncontrollably. Almost all children with Lennox-Gastaut syndrome develop learning problems and intellectual disability. Many also have delayed development of motor skills such as sitting and crawling. Most people with Lennox-Gastaut syndrome require help with usual activities of daily living.
- Dravet syndrome is a rare genetic condition that appears during the first year of life. With frequent fever-related seizures (febrile seizures). Later, other types of seizures typically arise, including myoclonic seizures (involuntary muscle spasms). Additionally, status epilepticus, a potentially life-threatening state of continuous seizure activity requiring emergency medical care, may occur. Children with Dravet syndrome typically experience poor development of language and motor skills, hyperactivity and difficulty relating to others.

Cannabidiol Oral Solution (CBD-OS) – Epidiolex

- Almost all patients with LGS and DS continue to have seizures despite treatment with multiple AEDs, putting them at high risk for injury or death. The primary goal of therapy for LGS and DS is to reduce seizure frequency and severity while limiting the AEs associated with multiple AEDs; however, there remains a significant unmet need for additional therapies for these patients.

Cannabidiol Oral Solution (CBD-OS) – Epidiolex

- Although CBD is a cannabinoid, it shares almost none of the pharmacologic features of the prototypical cannabinoid, Δ9-tetrahydrocannabinol (THC). In animal models of seizures, CBD is thought to exert its anticonvulsant effect by a reduction in neuronal hyperexcitability and inflammation through modulation of intracellular calcium via the orphan G protein-coupled receptor (GPR55) and the transient receptor potential channel 1 (TRPV1), as well as through modulation of adenosine-mediated signaling.
Cannabidiol Oral Solution (CBD-OS)– Epidiolex

- **Warnings and Precautions:**
  - Hepatocellular injury: monitor ALT, AST and bilirubin.
  - Somnolence and sedation: tends to be dose related and transient and is additive to other CNS depressants.
  - Suicidal ideation and behavior: as with other anticonvulsants monitor patients for suicidal thoughts and behavior.
  - Withdrawal of antiepileptic medications: gradually reduce dose over time to reduce risk of increased seizure frequency and/or status epilepticus.
  - Hypersensitivity reactions: including pruritis, erythema or angioedema (avoid in patients who are sensitive to cannabinol or any ingredient including sesame oil).

Indications: treatment of seizures in patients with Lennox-Gastaut syndrome or Dravet syndrome in patients two years of age or older.

Available as 100 mg/ml in 100 ml clear/yellowish solution, expires 12 weeks after opening.

**Dosing Information:**
- **EPIDIOLEX** is to be administered orally.
- The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day).
- After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day).
- Patients who are tolerating EPIDIOLEX at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated. For patients who are using comedication from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increased in a more frequent manner than every other day. Administration of the 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates than the recommended maintenance dosage of 10 mg/kg/day, but with an increase in adverse reactions.

When taken with high fat/high calorie food the C-max is increased 5 fold and the AUC is increased 4 fold.

**Cannabidiol Oral Solution (CBD-OS)– Epidiolex**

<table>
<thead>
<tr>
<th>Hepatic Impairment</th>
<th>Starting Dosage</th>
<th>Maintenance Dosage</th>
<th>Maximum Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>2.5 mg/kg twice daily (5 mg/kg/day)</td>
<td>5 mg/kg twice daily (10 mg/kg/day)</td>
<td>10 mg/kg twice daily (20 mg/kg/day)</td>
</tr>
<tr>
<td>MODERATE</td>
<td>1.25 mg/kg twice daily (2.5 mg/kg/day)</td>
<td>2.5 mg/kg twice daily (5 mg/kg/day)</td>
<td>5 mg/kg twice daily (10 mg/kg/day)</td>
</tr>
<tr>
<td>SEVERE</td>
<td>0.5 mg/kg twice daily (1 mg/kg/day)</td>
<td>1 mg/kg twice daily (2 mg/kg/day)</td>
<td>2 mg/kg twice daily (4 mg/kg/day)</td>
</tr>
</tbody>
</table>

**Mean Drug Take Drug Again Visual Analogue Scale Scores by Treatment (Completer Population)**

The human data from clinical studies show that, following the abrupt cessation of CBD-OS in patients in the clinical trial setting, no signals of physical dependence were detected according to the Cannabis Withdrawal Scale or Pediatric Cannabinoid Withdrawal Scale.

The first FDA-approved drug that contains a purified drug substance derived from marijuana. It is the first FDA approval of a drug for the treatment of patients with Dravet syndrome.

CBD is a chemical component of the Cannabis sativa plant, more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the “high”) that comes from tetrahydrocannabinol (THC).

It is THC (and not CBD) that is the primary psychoactive component of marijuana.

Should be available by mid November 2018 now that DEA has scheduled the drug as a C-V.
Nov. 11, 2017 FDA Drug Safety Communication Re-Febuxostat-Uloric CV Safety

- The febuxostat drug labels already carry a Warning and Precaution about cardiovascular events because the clinical trials conducted before approval showed a higher rate of heart-related problems in patients treated with febuxostat compared to allopurinol. These problems included heart attacks, strokes, and heart-related deaths. As a result, the FDA required an additional safety clinical trial after the drug was approved and on the market to better understand these differences, and that trial was finished recently.
- The CV safety trial was conducted in over 6,000 patients with gout treated with either febuxostat or allopurinol. The primary outcome was a combination of heart-related death, non-deadly heart attack, non-deadly stroke, and a condition of inadequate blood supply to the heart requiring urgent surgery. The preliminary results show that overall, febuxostat did not increase the risk of these combined events compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of heart-related deaths and death from all causes.

Risk Factors for Allopurinol Skin Reactions

- Allopurinol-associated cutaneous adverse reactions severe enough to require hospitalization occurred three to six times as often in Asians, blacks, and Native Hawaiians/Pacific Islanders than in whites or Hispanics, and up to 12 times as often in members of the high-risk groups who were also female and older than 60 years, researchers report in an article published online April 13 in the Annals of the Rheumatic Diseases. (Ann Rheum Dis 2018;0:1–7. doi:10.1136/annrheumdis-2017-212905).
- The elevated risk paralleled the frequency of the HLA-B*5801 allele in each ethnic/racial group, and higher risk was also associated with initial allopurinol dosing of more than 100 mg/day. Neither gout nor prior diuretic use was associated with increased risk.
- Recommend screening of Asian, black, and native Hawaiian/Pacific Islander patients for the presence of HLA-B*5801 before initiating allopurinol, particularly those who also have additional risk factors (female, age >60 years, or chronic kidney disease).

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout (NEJM on-line 3-12-2018)

- 6190 patients underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months (maximum, 85 months). CARES Trial
- In the modified intention-to-treat analysis, a primary end-point (the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina) event occurred in 335 patients (10.8%) in the febuxostat group and in 321 patients (10.4%) in the allopurinol group (hazard ratio, 1.03; upper limit of the one-sided 98.5% confidence interval [CI], 1.23; P=0.002 for noninferiority).
- All-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for cardiovascular death, 1.34 [95% CI, 1.03 to 1.73]).

New Drug Update

1. Which statement concerning the new Herpes Zoster sub-unit Vaccine (Shingrix) is NOT correct?
   - A. Vaccine efficacy is much higher with the new sub-unit vaccine (Shingrix) particularly in older adults as compared with the older live attenuated zoster vaccine (Zostavax).
   - B. The CDC has recommended the new vaccine as preferred for patients age 50 and older.
   - C. The sub-unit vaccine (Shingrix) is administered as a single dose sub Q.
   - D. Patients who have previously received a dose of the live attenuated vaccine (Zostavax) should also be immunized with the sub-unit vaccine (Shingrix) with at least 8 weeks between doses.
   - E. None of the above (All are correct).

2. Which medication(s) (CV Trial) is/are NOT preferred in the new 2018 American Diabetes Association (ADA) Standards of Care for patients with type 2 diabetes and established atherosclerotic cardiovascular disease: Antihyperglycemic therapy should begin with lifestyle management and metformin, and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality.
   - A. Empagliflozin (EMPA-REG OUTCOME Trial)
   - B. Liraglutide (LEADER Trial)
   - C. Extended release exenatide (EXSCEL Trial)
   - D. Lixisenatide (ELIXA Trial)
   - E. Both C and D