WEBVTT

- NOTE duration:"00:58:31"
- NOTE recognizability:0.806
- NOTE language:en-us
- NOTE Confidence: 0.85747489
- $00:00:00.000 \rightarrow 00:00:04.340$ Very kind introduction. By the way,
- NOTE Confidence: 0.85747489
- $00{:}00{:}04{.}340 \dashrightarrow 00{:}00{:}06{.}510$ you didn't hold me back in residency,
- NOTE Confidence: 0.85747489
- $00{:}00{:}06{.}510 \dashrightarrow 00{:}00{:}08{.}940$ except for may be the the raucous
- NOTE Confidence: 0.85747489
- $00:00:08.940 \dashrightarrow 00:00:11.790$ Halloween party. So I think that's
- NOTE Confidence: 0.85747489
- 00:00:11.790 --> 00:00:16.830 a topic for another. OK. Number.
- NOTE Confidence: 0.84460116
- $00:00:23.250 \longrightarrow 00:00:26.620$ So just get this reset.
- NOTE Confidence: 0.861854593333333
- $00{:}00{:}43.130 \dashrightarrow 00{:}00{:}47.798$ OK, and you can see the.
- NOTE Confidence: 0.861854593333333
- 00:00:47.800 --> 00:00:51.242 See. OK everyone OK, great.
- NOTE Confidence: 0.861854593333333
- 00:00:51.242 --> 00:00:55.090 Well you all I I think have varying
- NOTE Confidence: 0.861854593333333
- $00{:}00{:}55{.}204 \dashrightarrow 00{:}00{:}58{.}084$ degrees of familiarity with with
- NOTE Confidence: 0.861854593333333
- $00:00:58.084 \rightarrow 00:01:01.700$ what I'm going to talk about.
- NOTE Confidence: 0.861854593333333
- $00{:}01{:}01{.}700 \dashrightarrow 00{:}01{:}04{.}514$ You know in particular the the recent
- NOTE Confidence: 0.861854593333333
- $00{:}01{:}04{.}514 \dashrightarrow 00{:}01{:}06{.}878$ controversy in the news about the
- NOTE Confidence: 0.861854593333333

 $00:01:06.878 \rightarrow 00:01:09.121$ first so-called disease modifying

NOTE Confidence: 0.861854593333333

00:01:09.121 --> 00:01:11.629 the
rapies for Alzheimer's disease.

NOTE Confidence: 0.861854593333333

00:01:11.630 --> 00:01:13.580 Back in 2021, you know,

NOTE Confidence: 0.861854593333333

 $00:01:13.580 \longrightarrow 00:01:15.524$ they came to the news I'd you can't

NOTE Confidence: 0.861854593333333

 $00:01:15.530 \rightarrow 00:01:18.160$ approved the first disease modifying

NOTE Confidence: 0.861854593333333

 $00:01:18.160 \rightarrow 00:01:20.264$ therapy for Alzheimer's disease.

NOTE Confidence: 0.861854593333333

00:01:20.270 --> 00:01:21.850 But then immediately, well wait,

NOTE Confidence: 0.861854593333333

 $00:01:21.850 \longrightarrow 00:01:23.670$ it wasn't full approval.

NOTE Confidence: 0.861854593333333

 $00:01:23.670 \longrightarrow 00:01:26.980$ It was accelerated approval based on a

NOTE Confidence: 0.861854593333333

 $00:01:26.980 \longrightarrow 00:01:29.470$ biomarker and that's plaque clearance.

NOTE Confidence: 0.861854593333333

 $00:01:29.470 \longrightarrow 00:01:30.630$ And immediately there was,

NOTE Confidence: 0.861854593333333

00:01:30.630 --> 00:01:34.129 you know, a huge controversy.

NOTE Confidence: 0.861854593333333

 $00{:}01{:}34{.}130 \dashrightarrow 00{:}01{:}37{.}280$ Culminating about 10 months later in the

NOTE Confidence: 0.861854593333333

 $00:01:37.280 \rightarrow 00:01:40.650$ decision by CMS not to pay for the drug.

NOTE Confidence: 0.861854593333333

 $00:01:40.650 \longrightarrow 00:01:43.770$ And then as the dust settled for that,

NOTE Confidence: 0.861854593333333

 $00:01:43.770 \dashrightarrow 00:01:46.356$ we started to hear about lacanada

- NOTE Confidence: 0.861854593333333
- $00:01:46.356 \rightarrow 00:01:48.483$ different drug that actually appeared
- NOTE Confidence: 0.861854593333333
- $00{:}01{:}48{.}483 \dashrightarrow 00{:}01{:}51{.}147$ to meet the bar for full approval in
- NOTE Confidence: 0.861854593333333
- $00:01:51.147 \rightarrow 00:01:53.987$ in a in a more straightforward manner,
- NOTE Confidence: 0.861854593333333
- $00:01:53.990 \longrightarrow 00:01:55.922$ although as we're going to see the
- NOTE Confidence: 0.861854593333333
- $00{:}01{:}55{.}922 \dashrightarrow 00{:}01{:}57{.}562$ Kanab has its own uncertainties
- NOTE Confidence: 0.861854593333333
- $00:01:57.562 \dashrightarrow 00:01:59.806$ and some of its own controversies.
- NOTE Confidence: 0.861854593333333
- 00:01:59.810 --> 00:02:02.050 But all of that is what I'm going
- NOTE Confidence: 0.861854593333333
- $00:02:02.050 \longrightarrow 00:02:04.130$ to be talking about today.
- NOTE Confidence: 0.861854593333333
- $00:02:04.130 \longrightarrow 00:02:05.710$ Now this is my disclosure,
- NOTE Confidence: 0.861854593333333
- 00:02:05.710 --> 00:02:08.202 I'm going to be talking mainly about
- NOTE Confidence: 0.861854593333333
- 00:02:08.202 --> 00:02:10.029 the drugs aducanumab and lichen,
- NOTE Confidence: 0.861854593333333
- $00:02:10.030 \longrightarrow 00:02:10.402$ amab,
- NOTE Confidence: 0.861854593333333
- 00:02:10.402 --> 00:02:12.634 Yale and I received grant support
- NOTE Confidence: 0.861854593333333
- $00{:}02{:}12.634 \dashrightarrow 00{:}02{:}14.569$ for the conductive conduct of
- NOTE Confidence: 0.861854593333333
- $00:02:14.569 \longrightarrow 00:02:16.065$ trials with these drugs.
- NOTE Confidence: 0.861854593333333

 $00{:}02{:}16.070 \dashrightarrow 00{:}02{:}18.182$ And I'm also a paid consultant

NOTE Confidence: 0.861854593333333

00:02:18.182 $\operatorname{-->}$ 00:02:20.418 to Asahi who makes like canaman.

NOTE Confidence: 0.861854593333333

 $00{:}02{:}20{.}418 \dashrightarrow 00{:}02{:}23{.}123$ I don't have any any financial stake

NOTE Confidence: 0.861854593333333

 $00:02:23.123 \rightarrow 00:02:25.827$ in the in the success of these drugs.

NOTE Confidence: 0.861854593333333

 $00:02:25.830 \dashrightarrow 00:02:28.098$ And almost all of what I'm going to show

NOTE Confidence: 0.861854593333333

 $00:02:28.098 \rightarrow 00:02:30.366$ you is from peer reviewed publication,

NOTE Confidence: 0.861854593333333

 $00:02:30.370 \longrightarrow 00:02:32.182$ mainly that the New England Journal

NOTE Confidence: 0.861854593333333

 $00:02:32.182 \dashrightarrow 00:02:34.448$ article there about 2 exceptions to that.

NOTE Confidence: 0.861854593333333

00:02:34.450 --> 00:02:37.040 And I'll try to show you mention

NOTE Confidence: 0.861854593333333

 $00:02:37.040 \rightarrow 00:02:39.097$ when I'm showing you something

NOTE Confidence: 0.861854593333333

 $00:02:39.097 \longrightarrow 00:02:41.257$ that is not peer reviewed.

NOTE Confidence: 0.861854593333333

 $00:02:41.260 \dashrightarrow 00:02:44.316$ Well, so in in talking about like Canada,

NOTE Confidence: 0.861854593333333

 $00:02:44.320 \dashrightarrow 00:02:48.278$ I think we need to go back to the the whole

NOTE Confidence: 0.861854593333333

 $00:02:48.278 \rightarrow 00:02:52.094$ controversy with the earlier drug aducanumab.

NOTE Confidence: 0.861854593333333

 $00:02:52.100 \longrightarrow 00:02:55.076$ So there it was,

NOTE Confidence: 0.861854593333333

00:02:55.076 --> 00:02:56.500 June 7, 2021,

- NOTE Confidence: 0.861854593333333
- $00:02:56.500 \longrightarrow 00:02:58.200$ a day that would live.
- NOTE Confidence: 0.861854593333333
- 00:02:58.200 --> 00:02:59.138 You know,
- NOTE Confidence: 0.861854593333333
- $00{:}02{:}59{.}138 \dashrightarrow 00{:}03{:}01{.}952$ in something I'm almost concerned that
- NOTE Confidence: 0.861854593333333
- $00:03:01.952 \rightarrow 00:03:05.358$ they waited a day so they didn't try
- NOTE Confidence: 0.861854593333333
- $00:03:05.358 \rightarrow 00:03:07.740$ to eclipse the anniversary of D-Day,
- NOTE Confidence: 0.861854593333333
- $00:03:07.740 \longrightarrow 00:03:10.736$ but it was, it was huge news,
- NOTE Confidence: 0.861854593333333
- $00:03:10.740 \longrightarrow 00:03:12.375$ but then almost.
- NOTE Confidence: 0.861854593333333
- $00:03:12.375 \rightarrow 00:03:14.555$ Instantaneously came the backlash,
- NOTE Confidence: 0.861854593333333
- $00:03:14.560 \longrightarrow 00:03:15.600$ the controversy.
- NOTE Confidence: 0.861854593333333
- 00:03:15.600 --> 00:03:18.720 You know, that this was only,
- NOTE Confidence: 0.861854593333333
- 00:03:18.720 --> 00:03:20.916 you know, approval based on biomarker,
- NOTE Confidence: 0.861854593333333
- $00:03:20.920 \longrightarrow 00:03:23.539$ not full approval.
- NOTE Confidence: 0.861854593333333
- 00:03:23.540 --> 00:03:25.492 And I'm going to go into more of
- NOTE Confidence: 0.861854593333333
- $00{:}03{:}25{.}492 \dashrightarrow 00{:}03{:}27{.}358$ what the controversy was about.
- NOTE Confidence: 0.861854593333333
- $00:03:27.360 \dashrightarrow 00:03:30.522$ But I think to do that I need to do a
- NOTE Confidence: 0.861854593333333

 $00:03:30.522 \rightarrow 00:03:32.960$ little background on the pathogenesis

NOTE Confidence: 0.861854593333333

 $00{:}03{:}32{.}960 \dashrightarrow 00{:}03{:}36{.}500$ and mechanisms that underlie these drugs,

NOTE Confidence: 0.861854593333333

 $00:03:36.500 \longrightarrow 00:03:39.224$ and then more detail about the

NOTE Confidence: 0.861854593333333

 $00:03:39.224 \rightarrow 00:03:41.800$ actual evidence for and against.

NOTE Confidence: 0.861854593333333

00:03:41.800 --> 00:03:43.766 You can't,

NOTE Confidence: 0.861854593333333

 $00:03:43.766 \longrightarrow 00:03:44.749$ amab.

NOTE Confidence: 0.861854593333333

00:03:44.750 --> 00:03:47.130 So by way of background you know

NOTE Confidence: 0.861854593333333

 $00{:}03{:}47{.}130 \dashrightarrow 00{:}03{:}48{.}868$ these these are anti amyloid

NOTE Confidence: 0.861854593333333

00:03:48.868 --> 00:03:51.854 drugs and we need to look at the

NOTE Confidence: 0.861854593333333

 $00:03:51.854 \rightarrow 00:03:54.750$ mechanism of amyloid production.

NOTE Confidence: 0.861854593333333

 $00:03:54.750 \rightarrow 00:03:58.126$ So what we're looking at here is the

NOTE Confidence: 0.861854593333333

 $00:03:58.126 \rightarrow 00:04:01.089$ production of the toxic abeta peptide.

NOTE Confidence: 0.861854593333333

 $00:04:01.090 \longrightarrow 00:04:03.813$ I think you can see my cursor

NOTE Confidence: 0.861854593333333

 $00:04:03.813 \rightarrow 00:04:06.190$ from the the amyloid precursor

NOTE Confidence: 0.861854593333333

 $00:04:06.190 \longrightarrow 00:04:09.526$ protein over here on the left.

NOTE Confidence: 0.861854593333333

 $00:04:09.530 \rightarrow 00:04:14.786$ So this AP spans the the cell membrane then.

- NOTE Confidence: 0.861854593333333
- $00:04:14.790 \dashrightarrow 00:04:17.568$ The neuronal membrane in this case.
- NOTE Confidence: 0.861854593333333
- $00:04:17.570 \longrightarrow 00:04:20.132$ And it is cleaved by the
- NOTE Confidence: 0.861854593333333
- $00:04:20.132 \longrightarrow 00:04:21.840$ enzymes beta and gamma
- NOTE Confidence: 0.786859445
- $00:04:21.932 \dashrightarrow 00:04:25.924$ secret ase to form the toxic a beta fragment.
- NOTE Confidence: 0.786859445
- $00:04:25.930 \longrightarrow 00:04:28.930$ And exactly where where it's
- NOTE Confidence: 0.786859445
- 00:04:28.930 --> 00:04:31.330 cleave makes a difference,
- NOTE Confidence: 0.786859445
- $00:04:31.330 \longrightarrow 00:04:34.390$ where it's clear by gamma secretase.
- NOTE Confidence: 0.786859445
- $00:04:34.390 \longrightarrow 00:04:36.580$ And the main major forms as
- NOTE Confidence: 0.786859445
- $00:04:36.580 \longrightarrow 00:04:38.946$ we'll see are in a beta 42,
- NOTE Confidence: 0.786859445
- $00:04:38.946 \longrightarrow 00:04:40.210$ a little longer form.
- NOTE Confidence: 0.786859445
- $00:04:40.210 \longrightarrow 00:04:43.801$ And 40 it's a beta 42 that's
- NOTE Confidence: 0.786859445
- 00:04:43.801 --> 00:04:45.373 particularly malignant, amyloidogenic,
- NOTE Confidence: 0.786859445
- $00:04:45.373 \longrightarrow 00:04:48.088$ prone to aggregate into the.
- NOTE Confidence: 0.786859445
- 00:04:48.090 --> 00:04:50.370 Into the more toxic species
- NOTE Confidence: 0.786859445
- $00:04:50.370 \longrightarrow 00:04:52.194$ and what are those?
- NOTE Confidence: 0.786859445

 $00{:}04{:}52{.}200 \dashrightarrow 00{:}04{:}55{.}984$ Well, a lot of evidence is that those

NOTE Confidence: 0.786859445

00:04:55.984 --> 00:04:59.123 toxic species are soluble aggregated

NOTE Confidence: 0.786859445

 $00{:}04{:}59{.}123 \dashrightarrow 00{:}05{:}02{.}672$ species oligomers and and larger

NOTE Confidence: 0.786859445

 $00:05:02.672 \rightarrow 00:05:06.950$ oligomers referred to as proto fibrils.

NOTE Confidence: 0.786859445

00:05:06.950 --> 00:05:10.350 And all of these forms you know do

NOTE Confidence: 0.786859445

 $00:05:10.350 \dashrightarrow 00:05:13.109$ also aggregate further into plaques.

NOTE Confidence: 0.786859445

 $00{:}05{:}13.110 \dashrightarrow 00{:}05{:}14.174$ And overall,

NOTE Confidence: 0.786859445

 $00{:}05{:}14.174 \dashrightarrow 00{:}05{:}17.366$ the goal of these the rapies though

NOTE Confidence: 0.786859445

 $00{:}05{:}17.366 \dashrightarrow 00{:}05{:}21.270$ is to alter the balance between

NOTE Confidence: 0.786859445

 $00{:}05{:}21{.}270 \dashrightarrow 00{:}05{:}24{.}685$ production and clearance so the

NOTE Confidence: 0.786859445

 $00{:}05{:}24.685 \dashrightarrow 00{:}05{:}27.837$ antibodies aim to clear amyloid

NOTE Confidence: 0.786859445

 $00:05:27.837 \rightarrow 00:05:30.792$ and alter the balance favorably.

NOTE Confidence: 0.786859445

 $00:05:30.800 \rightarrow 00:05:34.058$ And what what are these antibodies?

NOTE Confidence: 0.786859445

 $00:05:34.060 \dashrightarrow 00:05:37.795$ Such as Lacan Amab and I do cannab.

NOTE Confidence: 0.786859445

00:05:37.800 --> 00:05:38.176 Well,

NOTE Confidence: 0.786859445

 $00:05:38.176 \longrightarrow 00:05:40.808$ that's that's shown here in in a

- NOTE Confidence: 0.786859445
- $00:05:40.808 \rightarrow 00:05:43.639$ somewhat busy table that I that I do

 $00:05:43.639 \rightarrow 00:05:45.990$ really want to simplify a great deal.

NOTE Confidence: 0.786859445

 $00:05:45.990 \rightarrow 00:05:50.966$ So these are in the case of aducanumab,

NOTE Confidence: 0.786859445

 $00:05:50.970 \rightarrow 00:05:54.134$ this is a an actual human antibody

NOTE Confidence: 0.786859445

 $00:05:54.134 \rightarrow 00:05:56.883$ was donated by 100 year old

NOTE Confidence: 0.786859445

00:05:56.883 - > 00:05:59.469 Swiss woman a few years back.

NOTE Confidence: 0.786859445

 $00:05:59.470 \dashrightarrow 00:06:02.510$ Been cloned and mass produced.

NOTE Confidence: 0.786859445

 $00{:}06{:}02.510 \dashrightarrow 00{:}06{:}05.270$ And now it's administered every four

NOTE Confidence: 0.786859445

 $00:06:05.270 \dashrightarrow 00:06:07.950$ weeks intravenously as a treatment.

NOTE Confidence: 0.786859445

 $00{:}06{:}07{.}950 \dashrightarrow 00{:}06{:}10.866$ Of note is that it's what we call an

NOTE Confidence: 0.786859445

 $00:06:10.870 \longrightarrow 00:06:15.886$ n-terminal antibody and the a beta

NOTE Confidence: 0.786859445

 $00{:}06{:}15.890 \dashrightarrow 00{:}06{:}18.585$ 42 is shown down here in purple.

NOTE Confidence: 0.786859445

 $00{:}06{:}18.590 \dashrightarrow 00{:}06{:}21.726$ You know the 42 amino acid structure and

NOTE Confidence: 0.786859445

 $00{:}06{:}21.726$ --> $00{:}06{:}24.956$ the end terminal is on the left side.

NOTE Confidence: 0.786859445

 $00:06:24.960 \rightarrow 00:06:27.648$ And so how'd you can't remember

- $00:06:27.648 \rightarrow 00:06:29.612$ by buying certain amino acids
- NOTE Confidence: 0.786859445
- $00:06:29.612 \longrightarrow 00:06:32.340$ 3 through 6 on the left side?
- NOTE Confidence: 0.786859445
- $00:06:32.340 \longrightarrow 00:06:35.112$ What's important about that is that even
- NOTE Confidence: 0.786859445
- $00:06:35.112 \rightarrow 00:06:38.080$ when amyloid is aggregated as oligomers,
- NOTE Confidence: 0.786859445
- $00:06:38.080 \longrightarrow 00:06:39.088$ proto fibrils,
- NOTE Confidence: 0.786859445
- $00:06:39.088 \longrightarrow 00:06:39.592$ plaques.
- NOTE Confidence: 0.786859445
- $00:06:39.592 \longrightarrow 00:06:42.616$ This portion of the of the
- NOTE Confidence: 0.786859445
- 00:06:42.616 --> 00:06:45.390 peptide is visible to antibodies,
- NOTE Confidence: 0.786859445
- $00{:}06{:}45{.}390 \dashrightarrow 00{:}06{:}47{.}034$ so they will still they will
- NOTE Confidence: 0.786859445
- $00{:}06{:}47.034 \dashrightarrow 00{:}06{:}48.709$ still target it and clear it.
- NOTE Confidence: 0.865366352857143
- $00{:}06{:}50{.}870 \dashrightarrow 00{:}06{:}53{.}187$ And over on the in the right
- NOTE Confidence: 0.865366352857143
- $00{:}06{:}53.187 \dashrightarrow 00{:}06{:}55.467$ columns you can see the big red,
- NOTE Confidence: 0.865366352857143
- $00:06:55.470 \longrightarrow 00:06:58.126$ yes for all of them are in fibral.
- NOTE Confidence: 0.865366352857143
- $00{:}06{:}58{.}130 \dashrightarrow 00{:}06{:}59{.}929$ So if it's an end terminal antibody,
- NOTE Confidence: 0.865366352857143
- $00:06:59.930 \longrightarrow 00:07:01.746$ that's why it targets
- NOTE Confidence: 0.865366352857143
- $00:07:01.746 \longrightarrow 00:07:03.108$ these aggregated species.

- NOTE Confidence: 0.865366352857143
- $00:07:03.110 \longrightarrow 00:07:05.330$ It actually doesn't target
- NOTE Confidence: 0.865366352857143
- $00:07:05.330 \longrightarrow 00:07:08.105$ target monomers to speak of.
- NOTE Confidence: 0.865366352857143
- $00:07:08.110 \longrightarrow 00:07:09.988$ And we can't. Amap is similar.
- NOTE Confidence: 0.865366352857143
- $00{:}07{:}09{.}990 \dashrightarrow 00{:}07{:}11{.}438$ It's different but similar.
- NOTE Confidence: 0.865366352857143
- 00:07:11.438 --> 00:07:13.248 So it's a humanized antibody.
- NOTE Confidence: 0.865366352857143
- 00:07:13.250 --> 00:07:14.468 It's, you know,
- NOTE Confidence: 0.865366352857143
- $00{:}07{:}14.468 \dashrightarrow 00{:}07{:}16.904$ derived from a mouse antibody but
- NOTE Confidence: 0.865366352857143
- $00:07:16.904 \dashrightarrow 00:07:19.160$ fully humanized and structure.
- NOTE Confidence: 0.865366352857143
- 00:07:19.160 --> 00:07:21.340 It's also end terminal binding
- NOTE Confidence: 0.865366352857143
- 00:07:21.340 --> 00:07:23.520 amino acids one through 16,
- NOTE Confidence: 0.865366352857143
- $00:07:23.520 \rightarrow 00:07:25.926$ and so it also binds oligomers
- NOTE Confidence: 0.865366352857143
- $00:07:25.926 \longrightarrow 00:07:28.480$ and proto fibrils in particular,
- NOTE Confidence: 0.865366352857143
- $00{:}07{:}28.480 \dashrightarrow 00{:}07{:}30.290$ and to some extent fibrils.
- NOTE Confidence: 0.73357914
- 00:07:34.070 --> 00:07:39.034 Now moving back to Umm aducanumab
- NOTE Confidence: 0.73357914
- $00:07:39.034 \longrightarrow 00:07:42.330$ and the aducanumab story.
- NOTE Confidence: 0.73357914

00:07:42.330 --> 00:07:44.836 So this drug, you know, was, you know,

NOTE Confidence: 0.73357914

 $00:07:44.836 \dashrightarrow 00:07:47.248$ developed over the last several years.

NOTE Confidence: 0.73357914

00:07:47.250 - 00:07:50.190 These are data from the original,

NOTE Confidence: 0.73357914

 $00{:}07{:}50{.}190 \dashrightarrow 00{:}07{:}52{.}570$ one of the original phase one studies,

NOTE Confidence: 0.73357914

 $00{:}07{:}52{.}570 \dashrightarrow 00{:}07{:}54{.}254$ a Phase 1B study.

NOTE Confidence: 0.73357914

 $00{:}07{:}54.254 \dashrightarrow 00{:}07{:}57.478$ And what we're looking at actually are NOTE Confidence: 0.73357914

 $00:07:57.478 \longrightarrow 00:08:00.543$ individual PET scans from individual

NOTE Confidence: 0.73357914

00:08:00.543 --> 00:08:03.935 participants who received you know either

NOTE Confidence: 0.73357914

 $00:08:03.935 \dashrightarrow 00:08:07.215$ placebo or progressively higher doses of NOTE Confidence: 0.73357914

00:08:07.215 --> 00:08:10.575 aducanumab over the over a one year trial. NOTE Confidence: 0.73357914

00:08:10.580 --> 00:08:13.616 And these images are horizontal transaxial NOTE Confidence: 0.73357914

 $00:08:13.616 \rightarrow 00:08:16.961$ through the brain and high amyloid

NOTE Confidence: 0.73357914

 $00{:}08{:}16{.}961 \dashrightarrow 00{:}08{:}20{.}480$ binding is shown in red followed by yellow.

NOTE Confidence: 0.73357914

 $00:08:20.480 \dashrightarrow 00:08:22.685$ So for example this person on the

NOTE Confidence: 0.73357914

 $00:08:22.685 \dashrightarrow 00:08:25.179$ top row was in the place bo group.

NOTE Confidence: 0.73357914

 $00:08:25.180 \longrightarrow 00:08:27.724$ And you can see that their baseline and

- NOTE Confidence: 0.73357914
- 00:08:27.724 --> 00:08:30.147 one year scans look pretty similar,

00:08:30.150 - 00:08:33.870 not much change being on placebo,

NOTE Confidence: 0.73357914

 $00:08:33.870 \rightarrow 00:08:36.118$ but with progressively higher

NOTE Confidence: 0.73357914

 $00:08:36.118 \longrightarrow 00:08:37.804$ doses of aducanumab,

NOTE Confidence: 0.73357914

00:08:37.810 --> 00:08:40.298 3 megs per keg, 6 megs per keg,

NOTE Confidence: 0.73357914

00:08:40.300 --> 00:08:43.756 10 megs per keg administered again as as

NOTE Confidence: 0.73357914

 $00{:}08{:}43.756 \dashrightarrow 00{:}08{:}47.317$ in infusions every four weeks you see

NOTE Confidence: 0.73357914

 $00:08:47.317 \rightarrow 00:08:49.927$ progressively more clearance of amyloid

NOTE Confidence: 0.73357914

00:08:50.011 - 00:08:53.027 signal and in fact in the bottom row,

NOTE Confidence: 0.73357914

 $00:08:53.030 \rightarrow 00:08:56.334$ the 10 milligram per kilogram dose which.

NOTE Confidence: 0.73357914

 $00:08:56.340 \longrightarrow 00:08:57.976$ Is the clinically relevant

NOTE Confidence: 0.73357914

 $00:08:57.976 \longrightarrow 00:09:00.430$ dose when all of sudden done,

NOTE Confidence: 0.73357914

 $00{:}09{:}00{.}430 \dashrightarrow 00{:}09{:}02{.}075$ this person scan is actually

NOTE Confidence: 0.73357914

 $00{:}09{:}02{.}075 \dashrightarrow 00{:}09{:}04{.}469$ normal at the end of the study.

NOTE Confidence: 0.73357914

 $00:09:04.470 \longrightarrow 00:09:06.166$ The bit of yellow you see here is

 $00{:}09{:}06{.}166 \dashrightarrow 00{:}09{:}08{.}269$ in the white matter and it's what

NOTE Confidence: 0.73357914

 $00:09:08.269 \rightarrow 00:09:09.889$ we would call nonspecific binding.

NOTE Confidence: 0.73357914

00:09:09.890 --> 00:09:11.948 But if if they entered the study

NOTE Confidence: 0.73357914

 $00{:}09{:}11{.}948 \dashrightarrow 00{:}09{:}12{.}830$ with the scan,

NOTE Confidence: 0.73357914

 $00:09:12.830 \dashrightarrow 00:09:14.720$ they would have not been allowed because

NOTE Confidence: 0.73357914

 $00{:}09{:}14.720 \dashrightarrow 00{:}09{:}16.956$ they didn't have evidence, you know,

NOTE Confidence: 0.73357914

 $00:09:16.956 \longrightarrow 00:09:20.267$ of of amyloid on their pet scan.

NOTE Confidence: 0.73357914

 $00:09:20.270 \rightarrow 00:09:22.260$ So very dramatic plaque clearance.

NOTE Confidence: 0.73357914

 $00{:}09{:}22.260 \dashrightarrow 00{:}09{:}23.580$ So this is something that we

NOTE Confidence: 0.73357914

 $00:09:23.580 \longrightarrow 00:09:24.830$ had never ever seen before,

NOTE Confidence: 0.73357914

 $00:09:24.830 \longrightarrow 00:09:25.610$ you know,

NOTE Confidence: 0.73357914

 $00:09:25.610 \rightarrow 00:09:26.780$ until this study.

NOTE Confidence: 0.7811683966666667

00:09:29.050 --> 00:09:31.756 And and you know Biogen was

NOTE Confidence: 0.7811683966666667

00:09:31.756 --> 00:09:33.109 understandably very excited.

NOTE Confidence: 0.7811683966666667

00:09:33.110 -> 00:09:34.710 They actually skipped phase two.

NOTE Confidence: 0.7811683966666667

 $00:09:34.710 \longrightarrow 00:09:36.158$ They went right from

- NOTE Confidence: 0.7811683966666667
- 00:09:36.158 --> 00:09:37.968 phase one to phase three,
- NOTE Confidence: 0.7811683966666667
- $00:09:37.970 \longrightarrow 00:09:40.906$ but maybe a mistake as we'll see later.
- NOTE Confidence: 0.7811683966666667
- $00{:}09{:}40{.}910 \dashrightarrow 00{:}09{:}43{.}148$ Now these now flash forward are
- NOTE Confidence: 0.7811683966666667
- $00:09:43.148 \longrightarrow 00:09:46.153$ data from one of the two pivotal
- NOTE Confidence: 0.7811683966666667
- $00:09:46.153 \dashrightarrow 00:09:48.533$ phase three trials called emerge.
- NOTE Confidence: 0.7811683966666667
- $00{:}09{:}48.540 \dashrightarrow 00{:}09{:}51.746$ Um and. What we're looking at here
- NOTE Confidence: 0.7811683966666667
- 00:09:51.746 --> 00:09:54.740 again is amyloid plaque clearance,
- NOTE Confidence: 0.7811683966666667
- $00:09:54.740 \rightarrow 00:09:57.106$ but now we're looking at it quantitatively
- NOTE Confidence: 0.7811683966666667
- $00{:}09{:}57{.}106 \dashrightarrow 00{:}09{:}59{.}649$ and this is now over a year and a
- NOTE Confidence: 0.7811683966666667
- 00:09:59.649 --> 00:10:01.878 half instead of a year 78 week trial.
- NOTE Confidence: 0.7811683966666667
- 00:10:01.880 --> 00:10:04.225 You can see that the place bo group
- NOTE Confidence: 0.7811683966666667
- $00{:}10{:}04.225 \dashrightarrow 00{:}10{:}06.352$ doesn't have much change in the
- NOTE Confidence: 0.7811683966666667
- 00:10:06.352 --> 00:10:08.458 amyloid binding over the 18 months,
- NOTE Confidence: 0.7811683966666667
- $00{:}10{:}08{.}460 \dashrightarrow 00{:}10{:}11{.}160$ but the relevant high dose group,
- NOTE Confidence: 0.7811683966666667
- $00:10:11.160 \rightarrow 00:10:14.044$ mostly 10 megs per kig in purple
- NOTE Confidence: 0.7811683966666667

 $00:10:14.044 \rightarrow 00:10:16.160$ has dramatic plaque clearance.

NOTE Confidence: 0.7811683966666667

00:10:16.160 --> 00:10:18.300 And again without going into

NOTE Confidence: 0.7811683966666667

 $00:10:18.300 \longrightarrow 00:10:20.012$ the quantitation in detail,

NOTE Confidence: 0.7811683966666667

 $00:10:20.020 \rightarrow 00:10:22.176$ suffice it to say that most of

NOTE Confidence: 0.7811683966666667

 $00:10:22.176 \longrightarrow 00:10:24.289$ these people had normal appearing.

NOTE Confidence: 0.7811683966666667

00:10:24.290 --> 00:10:25.748 Pet scans visually,

NOTE Confidence: 0.7811683966666667

 $00:10:25.748 \longrightarrow 00:10:29.150$ quantitatively at the end of the study.

NOTE Confidence: 0.7811683966666667

 $00:10:29.150 \longrightarrow 00:10:30.230$ But the question then is,

NOTE Confidence: 0.7811683966666667

 $00:10:30.230 \longrightarrow 00:10:33.308$ is that associated with clinical benefit,

NOTE Confidence: 0.7811683966666667

 $00:10:33.310 \longrightarrow 00:10:36.438$ so at least in the case of the?

NOTE Confidence: 0.807918553333333

 $00:10:38.580 \rightarrow 00:10:41.598$ Emerged study, the answer was yes.

NOTE Confidence: 0.807918553333333

 $00:10:41.600 \rightarrow 00:10:44.952$ So here we're looking at the the primary

NOTE Confidence: 0.807918553333333

 $00{:}10{:}44.952 \dashrightarrow 00{:}10{:}48.258$ outcome of this study called the Cdr SB,

NOTE Confidence: 0.807918553333333

00:10:48.260 --> 00:10:50.612 the clinical Dementia Rating scale some

NOTE Confidence: 0.807918553333333

 $00{:}10{:}50{.}612 \dashrightarrow 00{:}10{:}53{.}969$ of boxes and for for the many of you

NOTE Confidence: 0.807918553333333

 $00{:}10{:}53{.}969 \dashrightarrow 00{:}10{:}56{.}401$ who aren't familiar with that what that

- NOTE Confidence: 0.807918553333333
- 00:10:56.401 --> 00:10:58.977 is is it's very commonly used now as
- NOTE Confidence: 0.807918553333333
- $00{:}10{:}58{.}980 \dashrightarrow 00{:}11{:}01{.}976$ the primary outcome in in these trials.
- NOTE Confidence: 0.807918553333333
- $00{:}11{:}01{.}980 \dashrightarrow 00{:}11{:}05{.}620$ It's based on an interview with a partner
- NOTE Confidence: 0.807918553333333
- $00:11:05.620 \rightarrow 00:11:09.309$ caregiver as well as the patient participant.
- NOTE Confidence: 0.807918553333333
- $00:11:09.310 \longrightarrow 00:11:11.222$ Themselves, and it generates
- NOTE Confidence: 0.807918553333333
- $00:11:11.222 \longrightarrow 00:11:14.090$ scores in each of 6 domains.
- NOTE Confidence: 0.807918553333333
- $00:11:14.090 \rightarrow 00:11:15.570$ Three of them are cognitive,
- NOTE Confidence: 0.807918553333333
- 00:11:15.570 --> 00:11:17.394 three of them have to do
- NOTE Confidence: 0.807918553333333
- 00:11:17.394 --> 00:11:18.306 with daily functioning.
- NOTE Confidence: 0.807918553333333
- $00:11:18.310 \longrightarrow 00:11:21.310$ They're all scored zero to three.
- NOTE Confidence: 0.807918553333333
- $00:11:21.310 \longrightarrow 00:11:25.250$ So the overall Cdr SB score is 0 to 18,
- NOTE Confidence: 0.807918553333333
- $00{:}11{:}25{.}250 \dashrightarrow 00{:}11{:}27{.}890$ with higher scores being worse.
- NOTE Confidence: 0.807918553333333
- 00:11:27.890 --> 00:11:29.606 A 0 is a perfect score.
- NOTE Confidence: 0.76115661
- 00:11:31.670 --> 00:11:34.127 And people in this early AD group
- NOTE Confidence: 0.76115661
- $00:11:34.127 \longrightarrow 00:11:36.633$ that tend to be bunched with
- NOTE Confidence: 0.76115661

- $00:11:36.633 \rightarrow 00:11:38.794$ scores between 0.5 and about 6.
- NOTE Confidence: 0.76115661
- 00:11:38.794 --> 00:11:40.660 What you can see in this
- NOTE Confidence: 0.76115661
- 00:11:40.737 --> 00:11:42.329 in this study though,
- NOTE Confidence: 0.76115661
- $00:11:42.330 \longrightarrow 00:11:45.390$ is that the placebo group worsens
- NOTE Confidence: 0.76115661
- 00:11:45.390 00:11:47.406 over the course of a year and a half,
- NOTE Confidence: 0.76115661
- $00:11:47.410 \longrightarrow 00:11:49.996$ to the tune of about 1.75.
- NOTE Confidence: 0.76115661
- $00:11:49.996 \longrightarrow 00:11:53.764$ And the at height, the high dose side,
- NOTE Confidence: 0.76115661
- 00:11:53.764 --> 00:11:54.708 you can't imagine group,
- NOTE Confidence: 0.76115661
- $00:11:54.710 \rightarrow 00:11:58.130$ which is the relevant group, worsens as well,
- NOTE Confidence: 0.76115661
- $00:11:58.130 \longrightarrow 00:12:02.550$ but about .39 less than the placebo.
- NOTE Confidence: 0.76115661
- $00:12:02.550 \longrightarrow 00:12:05.446$ So that's the delta and that that is,
- NOTE Confidence: 0.76115661
- 00:12:05.450 --> 00:12:09.010 you know, statistically significant.
- NOTE Confidence: 0.76115661
- $00:12:09.010 \rightarrow 00:12:13.348$ And Umm and this, this is a positive study.
- NOTE Confidence: 0.76115661
- $00:12:13.350 \longrightarrow 00:12:14.734$ Now the problem is,
- NOTE Confidence: 0.76115661
- $00:12:14.734 \rightarrow 00:12:17.750$ is that the FDA requires two such studies
- NOTE Confidence: 0.76115661
- $00:12:17.750 \longrightarrow 00:12:19.430$ and Biogen had skipped phase two.

 $00:12:19.430 \rightarrow 00:12:22.090$ They might have gotten an opportunity there,

NOTE Confidence: 0.76115661

 $00{:}12{:}22.090 \dashrightarrow 00{:}12{:}24.176$ but they were required to have a

NOTE Confidence: 0.76115661

 $00:12:24.176 \longrightarrow 00:12:26.031$ sister study in phase three and

NOTE Confidence: 0.76115661

 $00{:}12{:}26.031 \dashrightarrow 00{:}12{:}28.694$ that was that was called engage

NOTE Confidence: 0.76115661

 $00:12:28.694 \rightarrow 00:12:32.650$ and here are the data for engage.

NOTE Confidence: 0.76115661

 $00{:}12{:}32.650 \dashrightarrow 00{:}12{:}35.744$ These are the data with the Cdr.

NOTE Confidence: 0.76115661

 $00:12:35.750 \rightarrow 00:12:39.166$ By the way engage also showed very robust.

NOTE Confidence: 0.76115661

00:12:39.170 --> 00:12:42.138 The amyloid plaque clearance on PET scan,

NOTE Confidence: 0.76115661

 $00:12:42.140 \longrightarrow 00:12:44.758$ when it came to the clinical measure,

NOTE Confidence: 0.76115661

 $00:12:44.760 \rightarrow 00:12:48.120$ the primary outcome, it was a total bust.

NOTE Confidence: 0.76115661

 $00{:}12{:}48.120 \dashrightarrow 00{:}12{:}51.110$ You know, there's nothing here.

NOTE Confidence: 0.76115661

 $00{:}12{:}51{.}110 \dashrightarrow 00{:}12{:}52{.}952$ The the worst line in purple

NOTE Confidence: 0.76115661

 $00:12:52.952 \longrightarrow 00:12:54.600$ is the high dose side.

NOTE Confidence: 0.76115661

00:12:54.600 --> 00:12:56.324 You can't amab group,

NOTE Confidence: 0.76115661

 $00{:}12{:}56{.}324 \dashrightarrow 00{:}12{:}58{.}048$ although it's trivially different

 $00:12:58.048 \rightarrow 00:12:59.929$ from the placebo group.

NOTE Confidence: 0.76115661

00:12:59.930 --> 00:13:02.918 So you know one positive and

NOTE Confidence: 0.76115661

 $00:13:02.918 \longrightarrow 00:13:04.910$ one very negative study.

NOTE Confidence: 0.76115661

 $00{:}13{:}04{.}910 \dashrightarrow 00{:}13{:}06{.}800$ Now, what to make of that,

NOTE Confidence: 0.76115661

 $00{:}13{:}06.800 \dashrightarrow 00{:}13{:}07.382$ you know,

NOTE Confidence: 0.76115661

 $00:13:07.382 \longrightarrow 00:13:08.837$ how could that possibly be?

NOTE Confidence: 0.8920642

00:13:10.980 - 00:13:15.125 So. This is before I really go into

NOTE Confidence: 0.8920642

 $00:13:15.125 \rightarrow 00:13:17.269$ this very scary looking figure,

NOTE Confidence: 0.8920642

00:13:17.270 --> 00:13:20.294 let me give you just a little background

NOTE Confidence: 0.8920642

 $00{:}13{:}20{.}294 \dashrightarrow 00{:}13{:}23{.}346$ that these studies emerge in again and

NOTE Confidence: 0.8920642

 $00:13:23.346 \rightarrow 00:13:26.389$ engage really went through quite an ordeal.

NOTE Confidence: 0.8920642

 $00:13:26.390 \longrightarrow 00:13:28.886$ One that many of you know is that

NOTE Confidence: 0.8920642

 $00:13:28.886 \rightarrow 00:13:31.011$ they were actually halted prematurely

NOTE Confidence: 0.8920642

 $00:13:31.011 \longrightarrow 00:13:33.849$ for a futility analysis which is

NOTE Confidence: 0.8920642

 $00{:}13{:}33{.}849 \dashrightarrow 00{:}13{:}36{.}837$ done commonly in our field where an

NOTE Confidence: 0.8920642

 $00{:}13{:}36{.}837 \dashrightarrow 00{:}13{:}38{.}988$ interim analysis looks at the data

- NOTE Confidence: 0.8920642
- $00:13:38.988 \longrightarrow 00:13:41.060$ fully up to a certain point and and
- NOTE Confidence: 0.8920642
- 00:13:41.125 --> 00:13:43.393 a judgment has made us about whether
- NOTE Confidence: 0.8920642
- $00:13:43.393 \rightarrow 00:13:45.490$ there's any chance chance of success.
- NOTE Confidence: 0.8920642
- $00{:}13{:}45{.}490 \dashrightarrow 00{:}13{:}48{.}154$ And the futility analysis indicated that
- NOTE Confidence: 0.8920642
- $00{:}13{:}48.154 \dashrightarrow 00{:}13{:}51.755$ that they were in fact futile and the
- NOTE Confidence: 0.8920642
- $00{:}13{:}51{.}755 \dashrightarrow 00{:}13{:}54{.}634$ studies were stopped and all the
- NOTE Confidence: 0.8920642
- $00:13:54.634 \rightarrow 00:13:56.589$ participants were brought in termination.
- NOTE Confidence: 0.8920642
- $00{:}13{:}56{.}590 \dashrightarrow 00{:}13{:}59{.}530$ Visits and so on and and it was a it
- NOTE Confidence: 0.8920642
- 00:13:59.618 --> 00:14:02.350 was a complete mistake, you know,
- NOTE Confidence: 0.8920642
- $00:14:02.350 \longrightarrow 00:14:04.050$ the futility analysis because
- NOTE Confidence: 0.8920642
- $00:14:04.050 \longrightarrow 00:14:06.430$ when all the data came in,
- NOTE Confidence: 0.8920642
- $00{:}14{:}06{.}430 \dashrightarrow 00{:}14{:}07{.}555$ and particularly there,
- NOTE Confidence: 0.8920642
- $00{:}14{:}07{.}555 \dashrightarrow 00{:}14{:}10{.}180$ there were three more months that had
- NOTE Confidence: 0.8920642
- $00{:}14{:}10.250 \dashrightarrow 00{:}14{:}12.562$ elapsed from the data cut point to the
- NOTE Confidence: 0.8920642
- $00{:}14{:}12{.}562 \dashrightarrow 00{:}14{:}15{.}178$ time all the data stopped being gathered.
- NOTE Confidence: 0.8920642

 $00:14:15.180 \rightarrow 00:14:18.237$ And and and obviously emerge will

NOTE Confidence: 0.8920642

 $00:14:18.237 \rightarrow 00:14:21.459$ emerge emerged as a positive study.

NOTE Confidence: 0.8920642

 $00{:}14{:}21{.}460 \dashrightarrow 00{:}14{:}24{.}452$ So and and without going into all of

NOTE Confidence: 0.8920642

 $00{:}14{:}24{.}452 \dashrightarrow 00{:}14{:}27{.}465$ the the reasons why the BIOSTATISTICIANS

NOTE Confidence: 0.8920642

 $00:14:27.465 \longrightarrow 00:14:31.160$ messed up which they which they did.

NOTE Confidence: 0.8920642

 $00:14:31.160 \longrightarrow 00:14:33.146$ There is yet another thing that

NOTE Confidence: 0.8920642

 $00:14:33.146 \rightarrow 00:14:35.451$ happened to these studies that was very

NOTE Confidence: 0.8920642

 $00:14:35.451 \rightarrow 00:14:37.380$ unfortunate and that is that Biogen

NOTE Confidence: 0.8920642

 $00{:}14{:}37{.}380 \dashrightarrow 00{:}14{:}39{.}780$ determined that the dosing they were

NOTE Confidence: 0.8920642

 $00{:}14{:}39{.}780 \dashrightarrow 00{:}14{:}42{.}542$ using for the studies was really not

NOTE Confidence: 0.8920642

 $00{:}14{:}42{.}542 \dashrightarrow 00{:}14{:}45{.}550$ not optimal and actually did a midstream.

NOTE Confidence: 0.8920642

 $00:14:45.550 \rightarrow 00:14:46.798$ Changing of dose.

NOTE Confidence: 0.8920642

 $00:14:46.798 \rightarrow 00:14:49.294$ And with that involved is originally

NOTE Confidence: 0.8920642

 $00:14:49.294 \rightarrow 00:14:51.968$ they had not felt everybody could

NOTE Confidence: 0.8920642

 $00{:}14{:}51{.}968 \dashrightarrow 00{:}14{:}54{.}153$ safely tolerate the high relevant

NOTE Confidence: 0.8920642

 $00:14:54.227 \rightarrow 00:14:55.919$ dose of 10 megs per kig.

- NOTE Confidence: 0.8920642
- $00:14:55.920 \rightarrow 00:14:58.594$ That's the dark blue in this figure.

 $00:14:58.600 \longrightarrow 00:14:58.892$ So,

NOTE Confidence: 0.8920642

 $00:14:58.892 \rightarrow 00:15:01.884$ so a lot of people who carry the APOE 4

NOTE Confidence: 0.8920642

 $00:15:01.884 \rightarrow 00:15:04.870$ gene were only going up to six megs per keg,

NOTE Confidence: 0.8920642

 $00:15:04.870 \longrightarrow 00:15:05.994$ which is, you know,

NOTE Confidence: 0.8920642

 $00:15:05.994 \longrightarrow 00:15:07.118$ ultimately determined to be,

NOTE Confidence: 0.8920642

00:15:07.120 --> 00:15:08.314 you know,

NOTE Confidence: 0.8920642

 $00:15:08.314 \longrightarrow 00:15:08.911$ subtherapeutic.

NOTE Confidence: 0.8920642

 $00{:}15{:}08{.}911 \dashrightarrow 00{:}15{:}12{.}842$ So they made a midstream adjustment and

NOTE Confidence: 0.8920642

00:15:12.842 --> 00:15:15.578 now what you would want now what what

NOTE Confidence: 0.8920642

 $00{:}15{:}15{.}578 \dashrightarrow 00{:}15{:}18{.}547$ these with this figure is showing you is.

NOTE Confidence: 0.8920642

00:15:18.550 --> 00:15:20.842 Individual level dosing for the high

NOTE Confidence: 0.8920642

 $00{:}15{:}20.842 \dashrightarrow 00{:}15{:}24.317$ dose arm of the study and only those

NOTE Confidence: 0.8920642

 $00{:}15{:}24.317 \dashrightarrow 00{:}15{:}26.647$ people assigned to active treatment,

NOTE Confidence: 0.8920642

 $00:15:26.650 \longrightarrow 00:15:27.686$ not placebo.

 $00:15:27.686 \rightarrow 00:15:31.312$ So what you really wanna see here

NOTE Confidence: 0.8920642

 $00:15:31.312 \longrightarrow 00:15:34.048$ is that from 24 weeks onward,

NOTE Confidence: 0.8920642

 $00{:}15{:}34.048 \dashrightarrow 00{:}15{:}36.750$ they should just be all dark blue.

NOTE Confidence: 0.8920642

 $00:15:36.750 \longrightarrow 00:15:37.730$ That would be the ideal.

NOTE Confidence: 0.8920642

 $00{:}15{:}37{.}730 \dashrightarrow 00{:}15{:}39{.}486$ Apart from early discontinuations,

NOTE Confidence: 0.8920642

 $00:15:39.486 \dashrightarrow 00:15:43.188$ it should just be a sea of dark blue.

NOTE Confidence: 0.8920642

 $00{:}15{:}43.190 \dashrightarrow 00{:}15{:}45.140$ But it's not.

NOTE Confidence: 0.8920642

 $00:15:45.140 \longrightarrow 00:15:46.196$ The yellow, you know,

NOTE Confidence: 0.8920642

 $00{:}15{:}46.196 \dashrightarrow 00{:}15{:}47.780$ a lot of people who who,

NOTE Confidence: 0.8920642

 $00{:}15{:}47.780 \dashrightarrow 00{:}15{:}49.604$ you know were early terminated for

NOTE Confidence: 0.8920642

 $00{:}15{:}49{.}604 \dashrightarrow 00{:}15{:}51{.}548$ futility and all of these lighter

NOTE Confidence: 0.8920642

 $00{:}15{:}51{.}548 \dashrightarrow 00{:}15{:}53{.}534$ shades are people who were still,

NOTE Confidence: 0.8920642

00:15:53.540 --> 00:15:54.334 you know,

NOTE Confidence: 0.8920642

 $00:15:54.334 \rightarrow 00:15:55.922$ mucking around with subtherapeutic

NOTE Confidence: 0.8920642

 $00{:}15{:}55{.}922 \dashrightarrow 00{:}15{:}57{.}900$ doses for a long time.

NOTE Confidence: 0.8920642

00:15:57.900 --> 00:16:00.400 And the argument Biogen made

- NOTE Confidence: 0.8920642
- $00{:}16{:}00{.}400 \dashrightarrow 00{:}16{:}03{.}418$ to the FTA is that, Umm,
- NOTE Confidence: 0.8920642
- 00:16:03.418 --> 00:16:04.454 you know,
- NOTE Confidence: 0.8920642
- 00:16:04.454 --> 00:16:04.972 is,
- NOTE Confidence: 0.8920642
- $00:16:04.972 \rightarrow 00:16:07.562$ is that this differentially impacted
- NOTE Confidence: 0.8920642
- $00{:}16{:}07{.}562 \dashrightarrow 00{:}16{:}10{.}717$ the two studies because in emerge
- NOTE Confidence: 0.8920642
- $00{:}16{:}10.720 \dashrightarrow 00{:}16{:}13.072$ 29% of people receive the full
- NOTE Confidence: 0.8920642
- $00:16:13.072 \rightarrow 00:16:15.490$ complement of the 10 milligram.
- NOTE Confidence: 0.8920642
- $00:16:15.490 \longrightarrow 00:16:18.521$ Kilogram doses and engage only 22%.
- NOTE Confidence: 0.8920642
- 00:16:18.521 $\operatorname{-->}$ 00:16:20.849 Did you know is that a big difference
- NOTE Confidence: 0.8920642
- $00{:}16{:}20{.}849 \dashrightarrow 00{:}16{:}23{.}106$ this had to do with the fact that
- NOTE Confidence: 0.8920642
- $00:16:23.106 \rightarrow 00:16:24.972$ that engage was an earlier timeline
- NOTE Confidence: 0.8920642
- $00{:}16{:}24{.}972 \dashrightarrow 00{:}16{:}26{.}940$ study and so it didn't benefit
- NOTE Confidence: 0.8920642
- $00:16:26.940 \longrightarrow 00:16:28.866$ as much from the modifications.
- NOTE Confidence: 0.8920642
- $00{:}16{:}28.866 \dashrightarrow 00{:}16{:}31.260$ But in any case the argument
- NOTE Confidence: 0.847965362777778
- $00{:}16{:}31{.}330 \dashrightarrow 00{:}16{:}32{.}990$ Biogen really tried to make
- NOTE Confidence: 0.847965362777778

 $00:16:32.990 \rightarrow 00:16:34.890$ to the FDA and the FDA,

NOTE Confidence: 0.847965362777778

00:16:34.890 --> 00:16:36.990 you know to some extent you know,

NOTE Confidence: 0.847965362777778

 $00:16:36.990 \rightarrow 00:16:39.244$ agreed was that if you just looked

NOTE Confidence: 0.847965362777778

 $00:16:39.244 \rightarrow 00:16:41.467$ at people who received the full

NOTE Confidence: 0.847965362777778

 $00{:}16{:}41{.}467 \dashrightarrow 00{:}16{:}43{.}447$ complement of doses both both

NOTE Confidence: 0.847965362777778

00:16:43.447 --> 00:16:45.648 studies you know should be nefit.

NOTE Confidence: 0.847965362777778

 $00{:}16{:}45.650 \dashrightarrow 00{:}16{:}47.468$ Unfortunately that's not how it works.

NOTE Confidence: 0.847965362777778

 $00{:}16{:}47{.}470 \dashrightarrow 00{:}16{:}49{.}290$ When you talk about a phase three

NOTE Confidence: 0.847965362777778

 $00:16:49.290 \rightarrow 00:16:50.479$ registration trial with the FDA,

NOTE Confidence: 0.847965362777778

 $00:16:50.480 \longrightarrow 00:16:51.800$ you don't get to do these

NOTE Confidence: 0.847965362777778

 $00:16:51.800 \longrightarrow 00:16:53.090$ you know post doc things.

NOTE Confidence: 0.847965362777778

00:16:53.090 --> 00:16:54.548 You've got to, you've got to,

NOTE Confidence: 0.847965362777778

 $00:16:54.550 \longrightarrow 00:16:56.668$ you've got to pre specify and

NOTE Confidence: 0.847965362777778

 $00:16:56.668 \rightarrow 00:16:59.575$ you've got to meet your aims and and

NOTE Confidence: 0.847965362777778

00:16:59.575 --> 00:17:02.070 clearly you know one study did not.

NOTE Confidence: 0.847965362777778

 $00:17:02.070 \rightarrow 00:17:05.955$ So then just to summarize the aducanumab

- NOTE Confidence: 0.847965362777778
- 00:17:05.955 --> 00:17:08.122 controversy here in this slide,
- NOTE Confidence: 0.847965362777778
- 00:17:08.122 --> 00:17:10.540 you know we had FDA approval
- NOTE Confidence: 0.847965362777778
- $00:17:10.624 \longrightarrow 00:17:13.192$ June of 21 via the accelerated
- NOTE Confidence: 0.847965362777778
- $00:17:13.192 \rightarrow 00:17:15.830$ pathway based on the biomarker.
- NOTE Confidence: 0.847965362777778
- $00{:}17{:}15.830 \dashrightarrow 00{:}17{:}16.910$ That was unvalidated.
- NOTE Confidence: 0.847965362777778
- $00{:}17{:}16{.}910 \dashrightarrow 00{:}17{:}19{.}987$ You know to that point this was completely
- NOTE Confidence: 0.847965362777778
- $00{:}17{:}19{.}987 \dashrightarrow 00{:}17{:}22{.}885$ against the recommendation of the FDA
- NOTE Confidence: 0.847965362777778
- $00{:}17{:}22.885 \dashrightarrow 00{:}17{:}25.599$ Advisory Committee who voted 8 to one
- NOTE Confidence: 0.847965362777778
- $00{:}17{:}25{.}599 \dashrightarrow 00{:}17{:}27{.}538$ against many of them resigned you know,
- NOTE Confidence: 0.847965362777778
- 00:17:27.540 --> 00:17:31.546 in protest after the approval and then you
- NOTE Confidence: 0.847965362777778
- $00:17:31.546 \rightarrow 00:17:35.099$ go ten months later and and CMS does a,
- NOTE Confidence: 0.847965362777778
- 00:17:35.100 -> 00:17:37.823 you know a fairly unusual makes a
- NOTE Confidence: 0.847965362777778
- $00:17:37.823 \rightarrow 00:17:40.052$ fairly unusual decision not to pay
- NOTE Confidence: 0.847965362777778
- 00:17:40.052 --> 00:17:42.020 for the drug despite FDA approval
- NOTE Confidence: 0.847965362777778
- $00:17:42.020 \longrightarrow 00:17:44.128$ and they indicate they're only
- NOTE Confidence: 0.847965362777778

- $00:17:44.128 \longrightarrow 00:17:45.836$ going to even consider.
- NOTE Confidence: 0.847965362777778
- 00:17:45.840 --> 00:17:46.271 Traditional,
- NOTE Confidence: 0.847965362777778
- $00:17:46.271 \longrightarrow 00:17:47.564$ full traditional approval
- NOTE Confidence: 0.847965362777778
- $00:17:47.564 \rightarrow 00:17:49.288$ based on clinical measures,
- NOTE Confidence: 0.847965362777778
- $00{:}17{:}49{.}290 \dashrightarrow 00{:}17{:}51{.}660$ not biomarkers and only under in
- NOTE Confidence: 0.847965362777778
- $00{:}17{:}51.660 \dashrightarrow 00{:}17{:}54.708$ in in a research context coverage
- NOTE Confidence: 0.847965362777778
- $00{:}17{:}54.708 \dashrightarrow 00{:}17{:}56.787$ with evidence development.
- NOTE Confidence: 0.847965362777778
- $00{:}17{:}56.790 \dashrightarrow 00{:}17{:}59.480$ So that's where that stood.
- NOTE Confidence: 0.847965362777778
- $00:17:59.480 \rightarrow 00:18:01.850$ And you know Biogen then subsequently
- NOTE Confidence: 0.847965362777778
- $00:18:01.850 \rightarrow 00:18:04.259$ you know launched yet another study
- NOTE Confidence: 0.847965362777778
- $00:18:04.259 \rightarrow 00:18:06.556$ which you know which they they
- NOTE Confidence: 0.847965362777778
- 00:18:06.556 --> 00:18:08.884 really needed to call Envision and
- NOTE Confidence: 0.847965362777778
- $00:18:08.884 \rightarrow 00:18:12.156$ this is the attempt to have a second
- NOTE Confidence: 0.847965362777778
- $00:18:12.156 \longrightarrow 00:18:14.680$ positive study that's done under the
- NOTE Confidence: 0.847965362777778
- 00:18:14.680 --> 00:18:17.260 accelerated pathway as a confirmatory study.
- NOTE Confidence: 0.847965362777778
- 00:18:17.260 --> 00:18:18.955 Although practically in this case

- NOTE Confidence: 0.847965362777778
- 00:18:18.955 --> 00:18:21.399 it's really you know and I think an
- NOTE Confidence: 0.847965362777778
- $00:18:21.399 \longrightarrow 00:18:23.374$ attempt to have a redo on on full
- NOTE Confidence: 0.847965362777778
- $00:18:23.374 \rightarrow 00:18:24.954$ approval and so they're they're
- NOTE Confidence: 0.847965362777778
- 00:18:24.954 --> 00:18:27.651 trying to do this you know fairly
- NOTE Confidence: 0.847965362777778
- $00:18:27.651 \longrightarrow 00:18:29.559$ launch it fairly rapidly.
- NOTE Confidence: 0.847965362777778
- $00:18:29.560 \longrightarrow 00:18:32.233$ And then at the end of this past year,
- NOTE Confidence: 0.847965362777778
- $00:18:32.240 \longrightarrow 00:18:33.920$ many of you may have seen that
- NOTE Confidence: 0.847965362777778
- $00:18:33.920 \rightarrow 00:18:35.899$ there was a congressional report.
- NOTE Confidence: 0.847965362777778
- $00:18:35.900 \longrightarrow 00:18:38.665$ That found the whole process
- NOTE Confidence: 0.847965362777778
- 00:18:38.665 --> 00:18:40.877 was rife with irregularities.
- NOTE Confidence: 0.847965362777778
- 00:18:40.880 --> 00:18:42.530 I mean the FDA and Biogen,
- NOTE Confidence: 0.847965362777778
- 00:18:42.530 --> 00:18:43.534 you know,
- NOTE Confidence: 0.847965362777778
- $00:18:43.534 \rightarrow 00:18:45.507$ we're really investigated including
- NOTE Confidence: 0.847965362777778
- $00{:}18{:}45{.}507 \dashrightarrow 00{:}18{:}47{.}842$ that there was this unusual
- NOTE Confidence: 0.847965362777778
- $00{:}18{:}47.842 \dashrightarrow 00{:}18{:}50.245$ collaborative work stream where FDA
- NOTE Confidence: 0.847965362777778

 $00:18:50.245 \rightarrow 00:18:52.560$ officials met repeatedly with Biogen,

NOTE Confidence: 0.847965362777778

00:18:52.560 --> 00:18:54.600 you know, to analyze trial data,

NOTE Confidence: 0.847965362777778

00:18:54.600 --> 00:18:55.766 you know,

NOTE Confidence: 0.847965362777778

 $00:18:55.766 \rightarrow 00:18:56.349$ mutually.

NOTE Confidence: 0.889060043333333

 $00:18:58.540 \longrightarrow 00:19:01.144$ All right. Well, and so it was

NOTE Confidence: 0.889060043333333

 $00:19:01.144 \longrightarrow 00:19:04.295$ in the wake of all of this that

NOTE Confidence: 0.889060043333333

00:19:04.295 --> 00:19:06.780 along came the news last fall,

NOTE Confidence: 0.889060043333333

00:19:06.780 --> 00:19:09.228 you know, initially kind of quietly.

NOTE Confidence: 0.889060043333333

00:19:09.230 --> 00:19:11.575 That a similar drug lacanau

NOTE Confidence: 0.889060043333333

 $00{:}19{:}11{.}575 \dashrightarrow 00{:}19{:}13{.}920$ amab appeared actually to meet

NOTE Confidence: 0.889060043333333

 $00:19:14.003 \longrightarrow 00:19:16.427$ the bar for full approval.

NOTE Confidence: 0.889060043333333

 $00:19:16.430 \longrightarrow 00:19:18.593$ You know, based on on results those

NOTE Confidence: 0.889060043333333

00:19:18.593 --> 00:19:20.460 press released in late September,

NOTE Confidence: 0.889060043333333

 $00:19:20.460 \longrightarrow 00:19:23.470$ fully presented at the end of November

NOTE Confidence: 0.889060043333333

 $00:19:23.470 \longrightarrow 00:19:26.289$ and appeared online in the New England

NOTE Confidence: 0.889060043333333

 $00{:}19{:}26.289 \dashrightarrow 00{:}19{:}29.002$ Journal at around that time at the

- NOTE Confidence: 0.889060043333333
- 00:19:29.002 --> 00:19:31.287 print publication just January 5.
- NOTE Confidence: 0.889060043333333
- $00{:}19{:}31{.}290 \dashrightarrow 00{:}19{:}33{.}442$ And for the rest of this talk I'm
- NOTE Confidence: 0.889060043333333
- 00:19:33.442 --> 00:19:35.266 really going to focus on you know,
- NOTE Confidence: 0.889060043333333
- $00:19:35.270 \longrightarrow 00:19:36.565$ this publication you know and
- NOTE Confidence: 0.889060043333333
- $00{:}19{:}36{.}565 \dashrightarrow 00{:}19{:}37{.}860$ and the data in it.
- NOTE Confidence: 0.72081560625
- 00:19:40.450 --> 00:19:43.370 So the Kanab, you know one more time,
- NOTE Confidence: 0.72081560625
- $00:19:43.370 \longrightarrow 00:19:44.708$ this is a busy slide.
- NOTE Confidence: 0.72081560625
- $00:19:44.710 \longrightarrow 00:19:47.038$ I'm really just focusing on the
- NOTE Confidence: 0.72081560625
- 00:19:47.038 --> 00:19:49.705 lower right and the red font that
- NOTE Confidence: 0.72081560625
- 00:19:49.705 --> 00:19:52.106 lichen amab you know again is a
- NOTE Confidence: 0.72081560625
- 00:19:52.184 --> 00:19:54.982 humanized IG1 monoclonal antibody.
- NOTE Confidence: 0.72081560625
- $00{:}19{:}54{.}982 \dashrightarrow 00{:}19{:}57{.}798$ It's selectively binds to
- NOTE Confidence: 0.72081560625
- $00{:}19{:}57.798 \dashrightarrow 00{:}19{:}59.910$ soluble aggregated species,
- NOTE Confidence: 0.72081560625
- $00{:}19{:}59{.}910 \dashrightarrow 00{:}20{:}02{.}310$ you know oligomers and proto fibrils.
- NOTE Confidence: 0.72081560625
- $00:20:02.310 \longrightarrow 00:20:05.810$ It's got 1000 fold selectivity for those
- NOTE Confidence: 0.72081560625

 $00{:}20{:}05{.}810 \dashrightarrow 00{:}20{:}08{.}493$ species over monomers and it even has

NOTE Confidence: 0.72081560625

 $00{:}20{:}08{.}493 \dashrightarrow 00{:}20{:}10{.}026$ a tenfold selectivity over fibrils.

NOTE Confidence: 0.72081560625

 $00{:}20{:}10.026 \dashrightarrow 00{:}20{:}12.540$ That are in plaque so that we know it.

NOTE Confidence: 0.72081560625

00:20:12.540 --> 00:20:14.636 It binds plaques because as you'll see it,

NOTE Confidence: 0.72081560625

 $00{:}20{:}14.640 \dashrightarrow 00{:}20{:}18.648$ it clears amyloid plaque on a PET scan.

NOTE Confidence: 0.72081560625

00:20:18.650 --> 00:20:21.476 Here's the Clarity AD study design

NOTE Confidence: 0.72081560625

00:20:21.476 --> 00:20:25.710 and and by the way I one thing I

NOTE Confidence: 0.72081560625

00:20:25.710 --> 00:20:27.840 should I should probably provide

NOTE Confidence: 0.72081560625

 $00:20:27.840 \longrightarrow 00:20:30.150$ clarity on which is that I'm only

NOTE Confidence: 0.72081560625

 $00:20:30.150 \longrightarrow 00:20:32.128$ going to show you one study,

NOTE Confidence: 0.72081560625

 $00:20:32.130 \longrightarrow 00:20:33.618$ I'm not going to show you

NOTE Confidence: 0.72081560625

 $00:20:33.618 \longrightarrow 00:20:34.610$ two studies right now.

NOTE Confidence: 0.72081560625

 $00:20:34.610 \longrightarrow 00:20:35.870$ Why is that?

NOTE Confidence: 0.72081560625

 $00{:}20{:}35{.}870 \dashrightarrow 00{:}20{:}38{.}810$ And it's because in this case you

NOTE Confidence: 0.72081560625

 $00{:}20{:}38{.}905 \dashrightarrow 00{:}20{:}41{.}360$ know the Canada went through very

NOTE Confidence: 0.72081560625

 $00:20:41.360 \rightarrow 00:20:43.853$ extensive phase two testing and their

00:20:43.853 --> 00:20:46.587 phase two study done in you know 850

NOTE Confidence: 0.72081560625

 $00{:}20{:}46.587 \dashrightarrow 00{:}20{:}49.506$ people which was actually a positive study.

NOTE Confidence: 0.72081560625

 $00:20:49.510 \rightarrow 00:20:52.598$ Still not a registration trial and so it

NOTE Confidence: 0.72081560625

 $00:20:52.598 \rightarrow 00:20:55.558$ was accepted as as a first positive study.

NOTE Confidence: 0.72081560625

 $00{:}20{:}55{.}560 \dashrightarrow 00{:}20{:}57{.}474$ So in this case the cannonade

NOTE Confidence: 0.72081560625

 $00:20:57.474 \rightarrow 00:20:59.422$ really needed to confirm that with

NOTE Confidence: 0.72081560625

 $00:20:59.422 \longrightarrow 00:21:01.234$ with a single large phase three

NOTE Confidence: 0.72081560625

 $00:21:01.234 \rightarrow 00:21:03.258$ trial and that that's the reason.

NOTE Confidence: 0.72081560625

 $00:21:03.260 \longrightarrow 00:21:06.748$ So in this study you can see that

NOTE Confidence: 0.72081560625

 $00:21:06.748 \rightarrow 00:21:10.196$ there were 1795 people who were

NOTE Confidence: 0.72081560625

 $00:21:10.196 \rightarrow 00:21:12.772$ randomized with early Alzheimer's

NOTE Confidence: 0.72081560625

 $00{:}21{:}12.772 \dashrightarrow 00{:}21{:}17.534$ and that means MC I you know or

NOTE Confidence: 0.72081560625

 $00{:}21{:}17.534$ --> $00{:}21{:}19.578$ prodromal Alzheimer's or mild.

NOTE Confidence: 0.72081560625

00:21:19.578 --> 00:21:22.332 Alzheimer's dementia but the but the

NOTE Confidence: 0.72081560625

 $00:21:22.332 \rightarrow 00:21:26.010$ they had to be confirmed for Alzheimer's

 $00:21:26.010 \rightarrow 00:21:29.200$ pathogenesis by any amyloid PET scan.

NOTE Confidence: 0.72081560625

 $00:21:29.200 \longrightarrow 00:21:31.600$ They were randomized 1 to one

NOTE Confidence: 0.72081560625

 $00{:}21{:}31{.}600 \dashrightarrow 00{:}21{:}34{.}180$ to either like cannab or place bo

NOTE Confidence: 0.72081560625

 $00{:}21{:}34{.}180 \dashrightarrow 00{:}21{:}36{.}862$ like cannab dosed as 10 milligram

NOTE Confidence: 0.72081560625

00:21:36.862 --> 00:21:39.100 per kilogram every two weeks.

NOTE Confidence: 0.72081560625

 $00{:}21{:}39{.}100 \dashrightarrow 00{:}21{:}41{.}305$ So this is administered twice

NOTE Confidence: 0.72081560625

 $00{:}21{:}41{.}305 \dashrightarrow 00{:}21{:}44{.}570$ as often as that you can amount.

NOTE Confidence: 0.72081560625

 $00{:}21{:}44{.}570 \dashrightarrow 00{:}21{:}47{.}138$ And that was an 18 month trial and

NOTE Confidence: 0.72081560625

 $00{:}21{:}47{.}138 \dashrightarrow 00{:}21{:}50{.}052$ that at the end of that you know there

NOTE Confidence: 0.72081560625

 $00:21:50.052 \rightarrow 00:21:52.453$ is an open extension trial which

NOTE Confidence: 0.72081560625

 $00{:}21{:}52{.}453 \dashrightarrow 00{:}21{:}55{.}262$ is very much ongoing and that means

NOTE Confidence: 0.72081560625

 $00:21:55.262 \rightarrow 00:21:58.430$ everybody in this phase is on active drug,

NOTE Confidence: 0.72081560625

 $00{:}21{:}58{.}430 \dashrightarrow 00{:}22{:}00{.}758$ no more place bo and I'm not going to

NOTE Confidence: 0.72081560625

 $00{:}22{:}00{.}758$ --> $00{:}22{:}03{.}081$ the New England Journal paper doesn't

NOTE Confidence: 0.72081560625

 $00{:}22{:}03.081 \dashrightarrow 00{:}22{:}05.583$ cover the extension phase at all.

NOTE Confidence: 0.72081560625

 $00:22:05.590 \rightarrow 00:22:07.438$ I'm only going to mention it when

- NOTE Confidence: 0.72081560625
- $00:22:07.438 \longrightarrow 00:22:09.880$ it comes to some of the you know
- NOTE Confidence: 0.72081560625
- $00{:}22{:}09{.}880 \dashrightarrow 00{:}22{:}11{.}830$ publicized you know safety issues that
- NOTE Confidence: 0.72081560625
- $00:22:11.830 \rightarrow 00:22:13.937$ have come up in the extension phase.
- NOTE Confidence: 0.72081560625
- $00:22:13.940 \rightarrow 00:22:16.350$ And on the far right,
- NOTE Confidence: 0.72081560625
- $00{:}22{:}16.350 \dashrightarrow 00{:}22{:}19.320$ the outcome measures and so on,
- NOTE Confidence: 0.72081560625
- 00:22:19.320 --> 00:22:20.336 I'm not going to,
- NOTE Confidence: 0.72081560625
- 00:22:20.336 --> 00:22:21.860 I'm going to go into these
- NOTE Confidence: 0.72081560625
- $00:22:21.922 \longrightarrow 00:22:24.118$ individually over the next few slides.
- NOTE Confidence: 0.87420221
- $00{:}22{:}26.640 \dashrightarrow 00{:}22{:}31.784$ But before that, the this shows the subject
- NOTE Confidence: 0.87420221
- 00:22:31.784 --> 00:22:35.469 disposition and analysis populations.
- NOTE Confidence: 0.87420221
- $00:22:35.470 \longrightarrow 00:22:39.358$ So meaning that before we got to the 17195
- NOTE Confidence: 0.87420221
- $00{:}22{:}39{.}358 \dashrightarrow 00{:}22{:}41{.}686$ people who were randomized and treated,
- NOTE Confidence: 0.87420221
- $00:22:41.690 \rightarrow 00:22:44.910$ there were nearly 6000 who were screened.
- NOTE Confidence: 0.87420221
- $00{:}22{:}44{.}910 \dashrightarrow 00{:}22{:}47{.}558$ Most of them were not eligible for the
- NOTE Confidence: 0.87420221
- $00:22:47.558 \rightarrow 00:22:49.946$ reasons shown in the screen failure box.
- NOTE Confidence: 0.87420221

00:22:49.950 --> 00:22:53.526 You know, usually it's that they didn't have,

NOTE Confidence: 0.87420221

00:22:53.530 --> 00:22:55.450 you know, amyloid positivity on

NOTE Confidence: 0.87420221

 $00:22:55.450 \rightarrow 00:22:58.194$ pat or even more commonly that they

NOTE Confidence: 0.87420221

 $00:22:58.194 \rightarrow 00:23:00.456$ weren't quite in the right cognitive

NOTE Confidence: 0.87420221

 $00:23:00.456 \longrightarrow 00:23:02.630$ range for this early ad study.

NOTE Confidence: 0.87420221

 $00:23:02.630 \longrightarrow 00:23:05.134$ But in any case.

NOTE Confidence: 0.87420221

 $00{:}23{:}05{.}134 \dashrightarrow 00{:}23{:}07{.}914$ The 1795 who are randomized and treated

NOTE Confidence: 0.87420221

 $00:23:07.914 \rightarrow 00:23:09.773$ were then evenly divided between

NOTE Confidence: 0.87420221

 $00{:}23{:}09{.}773 \dashrightarrow 00{:}23{:}11{.}927$ the place bo and the lucama groups.

NOTE Confidence: 0.87420221

 $00{:}23{:}11{.}930 \dashrightarrow 00{:}23{:}16{.}140$ And in the place bo group 84.4 completed

NOTE Confidence: 0.87420221

 $00:23:16.140 \longrightarrow 00:23:19.110$ the full 18 month study but they

NOTE Confidence: 0.87420221

00:23:19.110 --> 00:23:21.030 can't amount Group A little less

NOTE Confidence: 0.87420221

 $00:23:21.030 \longrightarrow 00:23:23.232$ 81.2 that's typical and the reason

NOTE Confidence: 0.87420221

00:23:23.232 --> 00:23:25.670 is because of more side effects,

NOTE Confidence: 0.87420221

 $00{:}23{:}25.670 \dashrightarrow 00{:}23{:}27.974$ more adverse events you know as

NOTE Confidence: 0.87420221

 $00{:}23{:}27{.}974 \dashrightarrow 00{:}23{:}32{.}392$ shown in in these boxes and the the
- NOTE Confidence: 0.87420221
- $00:23:32.392 \longrightarrow 00:23:34.562$ populations of analysis are are

 $00{:}23{:}34{.}562 \dashrightarrow 00{:}23{:}37{.}486$ worth you know just mentioning for

NOTE Confidence: 0.87420221

 $00:23:37.486 \rightarrow 00:23:40.438$ for all efficacy measures we looked

NOTE Confidence: 0.87420221

 $00:23:40.520 \longrightarrow 00:23:42.980$ at what's called the modified.

NOTE Confidence: 0.87420221

 $00:23:42.980 \longrightarrow 00:23:44.636$ Intent to treat population.

NOTE Confidence: 0.87420221

 $00{:}23{:}44.636 \dashrightarrow 00{:}23{:}48.517$ And all that means is you have to have

NOTE Confidence: 0.87420221

 $00{:}23{:}48{.}517 \dashrightarrow 00{:}23{:}50{.}707$ some body who was randomized actually

NOTE Confidence: 0.87420221

00:23:50.707 --> 00:23:54.118 got at least a dose of the drug and

NOTE Confidence: 0.87420221

 $00{:}23{:}54{.}118$ --> $00{:}23{:}55{.}986$ actually had one follow-up assessment

NOTE Confidence: 0.87420221

00:23:55.986 --> 00:23:58.807 that you could you could analyze because

NOTE Confidence: 0.87420221

 $00{:}23{:}58{.}807 \dashrightarrow 00{:}24{:}01{.}260$ not every body gets dosed gets there.

NOTE Confidence: 0.87420221

 $00{:}24{:}01{.}260 \dashrightarrow 00{:}24{:}03{.}297$ They might have had to terminate early,

NOTE Confidence: 0.87420221

 $00:24:03.300 \longrightarrow 00:24:04.770$ you know for a side effect and

NOTE Confidence: 0.87420221

 $00{:}24{:}04.770 \dashrightarrow 00{:}24{:}06.500$ never had a follow-up assessment.

NOTE Confidence: 0.87420221

 $00:24:06.500 \longrightarrow 00:24:08.930$ So that's the population used

 $00:24:08.930 \longrightarrow 00:24:10.460$ for efficacy measures.

NOTE Confidence: 0.87420221

00:24:10.460 --> 00:24:13.060 The safety population is everybody,

NOTE Confidence: 0.87420221

00:24:13.060 --> 00:24:14.745 everybody who you know was

NOTE Confidence: 0.87420221

 $00{:}24{:}14.745 \dashrightarrow 00{:}24{:}15.756$ randomized and dosed.

NOTE Confidence: 0.8517360675

 $00{:}24{:}18.520 \dashrightarrow 00{:}24{:}22.150$ Now here are the baseline

NOTE Confidence: 0.8517360675

 $00:24:22.150 \longrightarrow 00:24:25.392$ characteristics of the 1795 people.

NOTE Confidence: 0.8517360675

 $00:24:25.392 \rightarrow 00:24:29.120$ As you can see, this was a global study,

NOTE Confidence: 0.8517360675

 $00:24:29.120 \longrightarrow 00:24:31.464$ although a majority of them were in the

NOTE Confidence: 0.8517360675

 $00{:}24{:}31{.}464 \dashrightarrow 00{:}24{:}33{.}789$ far right column in the United States.

NOTE Confidence: 0.8517360675

 $00{:}24{:}33.790 \dashrightarrow 00{:}24{:}36.463$ And just a couple of things to touch on.

NOTE Confidence: 0.8517360675

00:24:36.470 -> 00:24:38.948 It was a broad age range about,

NOTE Confidence: 0.8517360675

 $00:24:38.950 \longrightarrow 00:24:42.534$ I think 20% were underage 65

NOTE Confidence: 0.8517360675

 $00:24:42.534 \rightarrow 00:24:48.910$ and close to 15% were over 80.

NOTE Confidence: 0.8517360675

 $00:24:48.910 \longrightarrow 00:24:51.694$ The other thing of note here I want

NOTE Confidence: 0.8517360675

 $00{:}24{:}51.694 \dashrightarrow 00{:}24{:}54.789$ to call attention to is race and

NOTE Confidence: 0.8517360675

 $00:24:54.789 \longrightarrow 00:24:57.531$ ethnicity and that's because in

00:24:57.531 --> 00:24:59.967 our field we've done really a bad

NOTE Confidence: 0.8517360675

 $00:24:59.967 \rightarrow 00:25:03.184$ job of including populations that

NOTE Confidence: 0.8517360675

 $00:25:03.184 \rightarrow 00:25:07.374$ represent the United States population.

NOTE Confidence: 0.8517360675

 $00:25:07.380 \rightarrow 00:25:09.949$ It's a it's a really, really important thing.

NOTE Confidence: 0.8517360675

 $00{:}25{:}09{.}949 \dashrightarrow 00{:}25{:}14{.}109$ This trial actually did the best of any of NOTE Confidence: 0.8517360675

00:25:14.109 --> 00:25:17.181 any such similar trial that I'm aware of,

NOTE Confidence: 0.8517360675

 $00:25:17.190 \longrightarrow 00:25:18.675$ but still inadequate.

NOTE Confidence: 0.8517360675

00:25:18.675 --> 00:25:21.582 So as an example, you know,

NOTE Confidence: 0.8517360675

00:25:21.582 --> 00:25:24.106 in the United States 4.5%

NOTE Confidence: 0.8517360675

00:25:24.106 --> 00:25:26.810 of participants were black.

NOTE Confidence: 0.8517360675

 $00:25:26.810 \longrightarrow 00:25:28.102$ That's good for us,

NOTE Confidence: 0.8517360675

 $00{:}25{:}28{.}102 \dashrightarrow 00{:}25{:}29{.}717$ but it's it's woefully inadequate.

NOTE Confidence: 0.8517360675

 $00:25:29.720 \longrightarrow 00:25:30.910$ This should be, you know,

NOTE Confidence: 0.8517360675

00:25:30.910 --> 00:25:34.334 9 or 10% if you go by black

NOTE Confidence: 0.8517360675

 $00{:}25{:}34{.}334 \dashrightarrow 00{:}25{:}37{.}899$ seniors in the United States with.

- 00:25:37.900 --> 00:25:39.072 Hispanic ethnicity,
- NOTE Confidence: 0.8517360675
- $00:25:39.072 \longrightarrow 00:25:42.540$ we actually did well, this is,
- NOTE Confidence: 0.8517360675
- $00:25:42.540 \longrightarrow 00:25:46.271$ this is really good 22.5% because that
- NOTE Confidence: 0.8517360675
- $00:25:46.271 \rightarrow 00:25:48.756$ actually over represents Hispanics who,
- NOTE Confidence: 0.8517360675
- $00{:}25{:}48.760 \dashrightarrow 00{:}25{:}51.539$ who in the senior senior age groups
- NOTE Confidence: 0.8517360675
- $00:25:51.539 \longrightarrow 00:25:54.396$ would again be in the order of 10%.
- NOTE Confidence: 0.8517360675
- $00{:}25{:}54{.}400 \dashrightarrow 00{:}25{:}56{.}885$ But we still need to do better
- NOTE Confidence: 0.8517360675
- $00:25:56.885 \longrightarrow 00:25:59.389$ and it's an important issue.
- NOTE Confidence: 0.8517360675
- $00{:}25{:}59{.}390 \dashrightarrow 00{:}26{:}01{.}134$ With regard to other
- NOTE Confidence: 0.8517360675
- $00:26:01.134 \longrightarrow 00:26:02.006$ clinical characteristics,
- NOTE Confidence: 0.8517360675
- $00:26:02.010 \longrightarrow 00:26:05.034$ I won't go into all of these.
- NOTE Confidence: 0.8517360675
- 00:26:05.040 --> 00:26:05.688 You know,
- NOTE Confidence: 0.8517360675
- $00{:}26{:}05{.}688 \dashrightarrow 00{:}26{:}07{.}956$ most of these folks are really early,
- NOTE Confidence: 0.8517360675
- 00:26:07.960 --> 00:26:08.808 you know,
- NOTE Confidence: 0.8517360675
- $00:26:08.808 \rightarrow 00:26:11.776$ more MCI prodromal than they are dementia.
- NOTE Confidence: 0.8517360675
- $00:26:11.780 \longrightarrow 00:26:13.761$ Most of these people are are functionally

- NOTE Confidence: 0.8517360675
- $00:26:13.761 \rightarrow 00:26:15.558$ independent at the start of the study,
- NOTE Confidence: 0.8517360675
- 00:26:15.560 --> 00:26:17.240 you know, people who drive a car,
- NOTE Confidence: 0.8517360675
- $00:26:17.240 \longrightarrow 00:26:19.620$ who do their own finances,
- NOTE Confidence: 0.8517360675
- $00:26:19.620 \rightarrow 00:26:22.020$ who do cooking, manage their meds,
- NOTE Confidence: 0.8517360675
- $00:26:22.020 \longrightarrow 00:26:24.100$ that's the majority of people.
- NOTE Confidence: 0.8517360675
- $00:26:24.100 \longrightarrow 00:26:24.992$ This is really quite,
- NOTE Confidence: 0.8517360675
- 00:26:24.992 --> 00:26:26.342 you know, early stage,
- NOTE Confidence: 0.8517360675
- $00{:}26{:}26{.}342 \dashrightarrow 00{:}26{:}28{.}597$ although it includes some with
- NOTE Confidence: 0.8517360675
- $00{:}26{:}28{.}597 \dashrightarrow 00{:}26{:}31{.}140$ you know very mild dementia.
- NOTE Confidence: 0.8517360675
- $00{:}26{:}31{.}140 \dashrightarrow 00{:}26{:}33{.}126$ What we for status is another
- NOTE Confidence: 0.8517360675
- 00:26:33.126 --> 00:26:33.788 important thing.
- NOTE Confidence: 0.8517360675
- $00{:}26{:}33.790 \dashrightarrow 00{:}26{:}35.350$ For those of you not familiar,
- NOTE Confidence: 0.8517360675
- $00:26:35.350 \longrightarrow 00:26:37.653$ April 4 is the major genetic risk
- NOTE Confidence: 0.8517360675
- $00{:}26{:}37{.}653 \dashrightarrow 00{:}26{:}39{.}170$ factor for Alzheimer's disease.
- NOTE Confidence: 0.8517360675
- $00{:}26{:}39{.}170 \dashrightarrow 00{:}26{:}43{.}640$ You know, late onset Alzheimer's and.
- NOTE Confidence: 0.8517360675

 $00{:}26{:}43.640 \dashrightarrow 00{:}26{:}48.232$ And typically about 69% of all the

NOTE Confidence: 0.8517360675

 $00{:}26{:}48{.}232 \dashrightarrow 00{:}26{:}50{.}440$ participants carried the April 4 at

NOTE Confidence: 0.8517360675

 $00{:}26{:}50{.}519 \dashrightarrow 00{:}26{:}53{.}144$ least one copy apply 4 allele that

NOTE Confidence: 0.8517360675

 $00:26:53.144 \longrightarrow 00:26:55.279$ that compares to about maybe 15

NOTE Confidence: 0.8517360675

 $00:26:55.279 \longrightarrow 00:26:57.200$ to 20% in the general population.

NOTE Confidence: 0.8517360675

 $00{:}26{:}57{.}200 \dashrightarrow 00{:}26{:}59{.}749$ This is a very typical sample in this

NOTE Confidence: 0.8517360675

 $00:26:59.749 \rightarrow 00:27:02.240$ regard and we see that percent for you know,

NOTE Confidence: 0.8517360675

 $00:27:02.240 \rightarrow 00:27:05.840$ people who carry one copy versus.

NOTE Confidence: 0.8517360675

 $00{:}27{:}05{.}840 \dashrightarrow 00{:}27{:}07{.}470$ 2 copies of the homozygotes,

NOTE Confidence: 0.8517360675

 $00:27:07.470 \longrightarrow 00:27:09.402$ homozygotes for about

NOTE Confidence: 0.8517360675

 $00{:}27{:}09{.}402 \dashrightarrow 00{:}27{:}11{.}978$ 15.5% of the population.

NOTE Confidence: 0.8517360675

 $00:27:11.980 \longrightarrow 00:27:13.140$ And this is important,

NOTE Confidence: 0.8517360675

 $00:27:13.140 \longrightarrow 00:27:13.720$ you know,

NOTE Confidence: 0.8517360675

 $00:27:13.720 \longrightarrow 00:27:14.767$ as we'll see,

NOTE Confidence: 0.8517360675

 $00:27:14.767 \longrightarrow 00:27:16.163$ particularly as it relates

NOTE Confidence: 0.8517360675

 $00:27:16.163 \rightarrow 00:27:18.519$ to some of the safety issues,

- NOTE Confidence: 0.8517360675
- $00:27:18.520 \longrightarrow 00:27:21.664$ about a little more than half of people
- NOTE Confidence: 0.8517360675
- $00:27:21.664 \rightarrow 00:27:25.017$ were on an approved Alzheimer's drug
- NOTE Confidence: 0.8517360675
- $00{:}27{:}25.017 \dashrightarrow 00{:}27{:}28.731$ like a choline sterase inhibitor or memantine.
- NOTE Confidence: 0.8517360675
- 00:27:28.740 --> 00:27:32.450 So now I'm gonna jump into the.
- NOTE Confidence: 0.8517360675
- $00:27:32.450 \longrightarrow 00:27:34.290$ The top line efficacy
- NOTE Confidence: 0.8517360675
- $00:27:34.290 \longrightarrow 00:27:36.130$ endpoints for the study.
- NOTE Confidence: 0.8517360675
- 00:27:36.130 > 00:27:38.464 So again the primary endpoint is
- NOTE Confidence: 0.8517360675
- $00:27:38.464 \rightarrow 00:27:41.289$ just what it was for aducanumab,
- NOTE Confidence: 0.8517360675
- $00{:}27{:}41{.}290 \dashrightarrow 00{:}27{:}43{.}585$ it's the change from baseline
- NOTE Confidence: 0.8517360675
- $00:27:43.585 \longrightarrow 00:27:46.630$ at 18 months in the Cdr SB.
- NOTE Confidence: 0.8517360675
- $00{:}27{:}46.630 \dashrightarrow 00{:}27{:}48.716$ I'm also going to show you most
- NOTE Confidence: 0.8517360675
- $00{:}27{:}48.716 \dashrightarrow 00{:}27{:}50.604$ of the key secondary endpoints
- NOTE Confidence: 0.8517360675
- $00:27:50.604 \rightarrow 00:27:52.448$ shown on the right,
- NOTE Confidence: 0.8517360675
- $00{:}27{:}52.450 \dashrightarrow 00{:}27{:}54.795$ one of biomarker which is
- NOTE Confidence: 0.8517360675
- 00:27:54.795 --> 00:27:57.140 clearance of amyloid on PET
- NOTE Confidence: 0.785593378461538

 $00{:}27{:}57{.}237 \dashrightarrow 00{:}27{:}58{.}982$ scan and then clinical measures.

NOTE Confidence: 0.785593378461538

 $00{:}27{:}58{.}982 \dashrightarrow 00{:}28{:}01{.}054$ I'm, I'm only going to show you,

NOTE Confidence: 0.785593378461538

00:28:01.060 - 00:28:02.446 I'm not going to show you the

NOTE Confidence: 0.785593378461538

 $00:28:02.446 \longrightarrow 00:28:03.678$ adcoms for the sake of time.

NOTE Confidence: 0.785593378461538

 $00{:}28{:}03.680 \dashrightarrow 00{:}28{:}05.920$ I'm going to show you the pure cognitive

NOTE Confidence: 0.785593378461538

 $00{:}28{:}05{.}920 \dashrightarrow 00{:}28{:}07{.}350$ and functional measures though.

NOTE Confidence: 0.850666078636364

 $00:28:09.820 \rightarrow 00:28:12.220$ So, so this is perhaps you know really

NOTE Confidence: 0.850666078636364

 $00:28:12.220 \rightarrow 00:28:15.455$ the key slide you know of the whole

NOTE Confidence: 0.850666078636364

 $00:28:15.455 \rightarrow 00:28:17.339$ presentation regarding we can't amab,

NOTE Confidence: 0.850666078636364

 $00{:}28{:}17.340 \dashrightarrow 00{:}28{:}20.094$ you know these are the results for the the,

NOTE Confidence: 0.850666078636364

 $00:28:20.100 \rightarrow 00:28:23.268$ the primary outcome, the primary endpoint.

NOTE Confidence: 0.850666078636364

 $00:28:23.270 \rightarrow 00:28:26.230$ This is what makes it a positive study.

NOTE Confidence: 0.850666078636364

 $00{:}28{:}26{.}230 \dashrightarrow 00{:}28{:}30{.}251$ The CD RSB and you know this is

NOTE Confidence: 0.850666078636364

 $00{:}28{:}30{.}251 \dashrightarrow 00{:}28{:}33{.}264$ this is similar to what we saw for

NOTE Confidence: 0.850666078636364

 $00:28:33.264 \rightarrow 00:28:35.776$ aducanumab in emerge and engage except

NOTE Confidence: 0.850666078636364

 $00:28:35.776 \rightarrow 00:28:38.746$ you'll remember that that you know

- NOTE Confidence: 0.850666078636364
- $00:28:38.746 \rightarrow 00:28:40.964$ the the directionality was different
- NOTE Confidence: 0.850666078636364
- 00:28:40.964 --> 00:28:43.860 instead of you know up being bad now
- NOTE Confidence: 0.850666078636364
- $00{:}28{:}43{.}938 \dashrightarrow 00{:}28{:}46{.}809$ down is being bad and we we did that
- NOTE Confidence: 0.850666078636364
- $00:28:46.809 \rightarrow 00:28:49.068$ because that way you could look at
- NOTE Confidence: 0.850666078636364
- $00{:}28{:}49.068 \dashrightarrow 00{:}28{:}51.336$ all the slides I looked at all the
- NOTE Confidence: 0.850666078636364
- $00:28:51.336 \rightarrow 00:28:53.162$ figures in the study and down was
- NOTE Confidence: 0.850666078636364
- $00:28:53.162 \longrightarrow 00:28:55.146$ always bad but in any case that's how
- NOTE Confidence: 0.850666078636364
- $00:28:55.146 \rightarrow 00:28:57.019$ it's graphed and what you can see.
- NOTE Confidence: 0.850666078636364
- $00{:}28{:}57{.}020 \dashrightarrow 00{:}29{:}00{.}092$ Is that the place bo group worsens
- NOTE Confidence: 0.850666078636364
- $00:29:00.092 \rightarrow 00:29:02.750$ by 1.66 points over 18 months.
- NOTE Confidence: 0.850666078636364
- $00:29:02.750 \longrightarrow 00:29:04.928$ Not quite as much as in the end you
- NOTE Confidence: 0.850666078636364
- $00{:}29{:}04{.}928 \dashrightarrow 00{:}29{:}07{.}235$ can't map studies and the treated group.
- NOTE Confidence: 0.847906556
- $00:29:11.140 \longrightarrow 00:29:14.576$ 1.22 with a difference of 0.45 and
- NOTE Confidence: 0.847906556
- $00:29:14.576 \longrightarrow 00:29:17.066$ which is highly highly statistically
- NOTE Confidence: 0.847906556
- $00{:}29{:}17.066 \dashrightarrow 00{:}29{:}20.085$ significant and it represents a 27%
- NOTE Confidence: 0.847906556

 $00:29:20.085 \rightarrow 00:29:23.115$ slowing of decline at 18 months.

NOTE Confidence: 0.847906556

00:29:23.120 --> 00:29:25.460 Drug placebo differences are evident

NOTE Confidence: 0.847906556

 $00{:}29{:}25{.}460 \dashrightarrow 00{:}29{:}29{.}317$ as early as six months and they at

NOTE Confidence: 0.847906556

 $00:29:29.317 \longrightarrow 00:29:31.570$ least numerically widen. Thereafter.

NOTE Confidence: 0.88777143

 $00:29:33.760 \longrightarrow 00:29:35.056$ Now this is the,

NOTE Confidence: 0.88777143

00:29:35.056 - 00:29:37.520 this is a non peer reviewed slide,

NOTE Confidence: 0.88777143

 $00{:}29{:}37{.}520 \dashrightarrow 00{:}29{:}40{.}288$ but I wanted to to show this in

NOTE Confidence: 0.88777143

 $00{:}29{:}40{.}288 \dashrightarrow 00{:}29{:}42{.}703$ relation to these Cdr data because

NOTE Confidence: 0.88777143

00:29:42.703 --> 00:29:45.693 a lot of the controversy you know

NOTE Confidence: 0.88777143

 $00{:}29{:}45{.}693 \dashrightarrow 00{:}29{:}48{.}345$ about these kind of results is

NOTE Confidence: 0.88777143

00:29:48.345 --> 00:29:50.386 are they clinically meaningful,

NOTE Confidence: 0.88777143

 $00{:}29{:}50{.}386 \dashrightarrow 00{:}29{:}52{.}504$ they're highly, highly,

NOTE Confidence: 0.88777143

00:29:52.504 --> 00:29:53.916 statistically significant,

NOTE Confidence: 0.88777143

 $00:29:53.920 \longrightarrow 00:29:55.308$ but are they meaningful.

NOTE Confidence: 0.88777143

 $00{:}29{:}55{.}308 \dashrightarrow 00{:}29{:}57{.}390$ And I'm going to mention you

NOTE Confidence: 0.88777143

00:29:57.461 - 00:29:59.453 know as I go two or three ways

 $00{:}29{:}59{.}453 \dashrightarrow 00{:}30{:}01{.}984$ that at least I think about the

NOTE Confidence: 0.88777143

 $00:30:01.984 \dashrightarrow 00:30:03.556$ meaningfulness of the results.

NOTE Confidence: 0.88777143

 $00:30:03.560 \rightarrow 00:30:05.926$ And one way that I would commonly

NOTE Confidence: 0.88777143

 $00{:}30{:}05{.}926 \dashrightarrow 00{:}30{:}08{.}930$ explain to A to a patient or participant

NOTE Confidence: 0.88777143

 $00{:}30{:}08{.}930 \dashrightarrow 00{:}30{:}11.825$ is what's shown here and it has to

NOTE Confidence: 0.88777143

 $00{:}30{:}11.825 \dashrightarrow 00{:}30{:}13.932$ do with kind of a time savings.

NOTE Confidence: 0.88777143

 $00:30:13.940 \longrightarrow 00:30:17.268$ So that is that in the placebo group

NOTE Confidence: 0.88777143

 $00{:}30{:}17.268 \dashrightarrow 00{:}30{:}19.526$ the amount of deterioration that

NOTE Confidence: 0.88777143

 $00:30:19.526 \longrightarrow 00:30:23.340$ occurs at end of study at 18 months.

NOTE Confidence: 0.88777143

 $00{:}30{:}23{.}340 \dashrightarrow 00{:}30{:}25{.}698$ If the rates of decline continued

NOTE Confidence: 0.88777143

 $00{:}30{:}25.698 \dashrightarrow 00{:}30{:}28.803$ after 18 months as they as they are

NOTE Confidence: 0.88777143

 $00{:}30{:}28.803 \dashrightarrow 00{:}30{:}31.427$ to that point and that's that's an

NOTE Confidence: 0.88777143

 $00{:}30{:}31{.}427 \dashrightarrow 00{:}30{:}34{.}003$ if that's a that's a big assumption.

NOTE Confidence: 0.88777143

 $00{:}30{:}34.010 \dashrightarrow 00{:}30{:}35.314$ The actively treated groups

NOTE Confidence: 0.88777143

 $00:30:35.314 \longrightarrow 00:30:37.270$ will get to the same point,

 $00:30:37.270 \longrightarrow 00:30:39.790$ but they will get there about

NOTE Confidence: 0.88777143

 $00:30:39.790 \longrightarrow 00:30:41.190$ 7 1/2 months later.

NOTE Confidence: 0.88777143

 $00:30:41.190 \longrightarrow 00:30:44.030$ So in that sense it's like a 7 1/2

NOTE Confidence: 0.88777143

 $00:30:44.030 \rightarrow 00:30:46.350$ month time saving of a certain level of,

NOTE Confidence: 0.88777143

 $00:30:46.350 \longrightarrow 00:30:47.842$ you know,

NOTE Confidence: 0.88777143

00:30:47.842 --> 00:30:50.080 cognitive daily functioning.

NOTE Confidence: 0.88777143

 $00:30:50.080 \dashrightarrow 00:30:52.726$ A more conservative way by the way

NOTE Confidence: 0.88777143

 $00:30:52.726 \rightarrow 00:30:54.949$ than extrapolating is to interpolate.

NOTE Confidence: 0.88777143

 $00{:}30{:}54{.}950 \dashrightarrow 00{:}30{:}57{.}162$ And that's what shown in the other

NOTE Confidence: 0.88777143

00:30:57.162 --> 00:30:59.550 kind of blue line where you where

NOTE Confidence: 0.88777143

 $00{:}30{:}59{.}550 \dashrightarrow 00{:}31{:}01{.}608$ you asked the question at what

NOTE Confidence: 0.88777143

00:31:01.675 --> 00:31:03.811 point did the placebo people already NOTE Confidence: 0.88777143

 $00:31:03.811 \rightarrow 00:31:06.086$ get to the point where the lucama

NOTE Confidence: 0.88777143

 $00:31:06.086 \rightarrow 00:31:08.408$ people did at 18 months and that and NOTE Confidence: 0.88777143

00:31:08.408 --> 00:31:10.132 then you go backwards 5.3 months.

NOTE Confidence: 0.88777143

 $00:31:10.132 \rightarrow 00:31:12.134$ So that would be a more conservative,

 $00{:}31{:}12{.}140 \dashrightarrow 00{:}31{:}14{.}150$ you know estimate and probably may be

NOTE Confidence: 0.88777143

 $00:31:14.150 \longrightarrow 00:31:16.400$ the truth is somewhere in between one.

NOTE Confidence: 0.88777143

 $00:31:16.400 \longrightarrow 00:31:18.476$ One thing that's very clear though

NOTE Confidence: 0.88777143

 $00:31:18.476 \longrightarrow 00:31:20.130$ is that this kind of.

NOTE Confidence: 0.88777143

 $00:31:20.130 \longrightarrow 00:31:22.622$ Measure is very much related to how

NOTE Confidence: 0.88777143

 $00{:}31{:}22.622 \dashrightarrow 00{:}31{:}24.723$ long you're on the drug, right.

NOTE Confidence: 0.88777143

 $00{:}31{:}24.723 \dashrightarrow 00{:}31{:}27.227$ So and as we'll see at the very

NOTE Confidence: 0.88777143

 $00:31:27.227 \longrightarrow 00:31:29.188$ end of this presentation,

NOTE Confidence: 0.88777143

 $00:31:29.190 \longrightarrow 00:31:31.493$ you know we start to think about

NOTE Confidence: 0.88777143

 $00{:}31{:}31{.}493 \dashrightarrow 00{:}31{:}33{.}288$ treating people earlier and for many

NOTE Confidence: 0.88777143

 $00{:}31{:}33.288 \dashrightarrow 00{:}31{:}35.402$ years we may be able to think about

NOTE Confidence: 0.88777143

 $00{:}31{:}35{.}402 \dashrightarrow 00{:}31{:}37{.}663$ much bigger effects than any of these.

NOTE Confidence: 0.88777143

 $00{:}31{:}37{.}670 \dashrightarrow 00{:}31{:}41{.}390$ But you know this is this is a

NOTE Confidence: 0.88777143

 $00{:}31{:}41{.}390 \dashrightarrow 00{:}31{:}44{.}860$ speculation now we're back to real data.

NOTE Confidence: 0.88777143

 $00{:}31{:}44{.}860 \dashrightarrow 00{:}31{:}46{.}855$ And now I'm moving on to the

00:31:46.855 --> 00:31:47.710 key secondary outcome,

NOTE Confidence: 0.88777143

 $00:31:47.710 \longrightarrow 00:31:52.176$ starting with the biomarker amyloid pet.

NOTE Confidence: 0.88777143

 $00:31:52.180 \longrightarrow 00:31:55.246$ So just as we saw with aducanumab,

NOTE Confidence: 0.88777143

 $00{:}31{:}55{.}250 \dashrightarrow 00{:}31{:}56{.}098$ you know,

NOTE Confidence: 0.88777143

 $00:31:56.098 \longrightarrow 00:31:57.370$ which dramatically clears

NOTE Confidence: 0.88777143

00:31:57.370 --> 00:31:59.910 fibrillar amyloid on a PET scan,

NOTE Confidence: 0.88777143

 $00{:}31{:}59{.}910 \dashrightarrow 00{:}32{:}02{.}711$ the same is true with lacanada here

NOTE Confidence: 0.88777143

 $00:32:02.711 \longrightarrow 00:32:06.615$ in the 18 month study you can see

NOTE Confidence: 0.88777143

 $00{:}32{:}06.615 \dashrightarrow 00{:}32{:}09.105$ that people in the place bo group

NOTE Confidence: 0.88777143

 $00{:}32{:}09{.}105 \dashrightarrow 00{:}32{:}12{.}512$ had you know at least a little

NOTE Confidence: 0.88777143

 $00:32:12.512 \rightarrow 00:32:15.230$ numerical increase in amyloid binding,

NOTE Confidence: 0.88777143

 $00:32:15.230 \longrightarrow 00:32:17.560$ whereas those on the kinomap,

NOTE Confidence: 0.88777143

 $00:32:17.560 \longrightarrow 00:32:21.100$ you know steadily decreased.

NOTE Confidence: 0.88777143

 $00{:}32{:}21.100 \dashrightarrow 00{:}32{:}23.186$ There is the scale that I'm not

NOTE Confidence: 0.88777143

 $00{:}32{:}23.186 \dashrightarrow 00{:}32{:}25.384$ going to explain to you called a

NOTE Confidence: 0.88777143

 $00:32:25.384 \rightarrow 00:32:27.244$ centroid scale that is being used.

- NOTE Confidence: 0.88777143
- $00:32:27.250 \rightarrow 00:32:29.308$ This is a way of standardizing you

00:32:29.308 --> 00:32:31.460 know Emily PET data across studies,

NOTE Confidence: 0.88777143

 $00{:}32{:}31{.}460 \dashrightarrow 00{:}32{:}34{.}044$ across scanners, across radiopharmaceuticals.

NOTE Confidence: 0.88777143

 $00:32:34.044 \rightarrow 00:32:38.361$ But suffice it to say that you

NOTE Confidence: 0.88777143

 $00:32:38.361 \dashrightarrow 00:32:40.566$ know the drug place bo difference

NOTE Confidence: 0.88777143

00:32:40.566 --> 00:32:43.631 here was 59 centroids again highly

NOTE Confidence: 0.88777143

 $00:32:43.631 \longrightarrow 00:32:45.745$ significant but to make to

NOTE Confidence: 0.88777143

 $00:32:45.745 \longrightarrow 00:32:48.212$ to talk a little bit about what

NOTE Confidence: 0.88777143

 $00{:}32{:}48{.}212 \dashrightarrow 00{:}32{:}50{.}417$ what center Lloyd's you know.

NOTE Confidence: 0.860418372222222

 $00:32:50.420 \longrightarrow 00:32:50.918$ Represent.

NOTE Confidence: 0.860418372222222

 $00{:}32{:}50{.}918 \dashrightarrow 00{:}32{:}54{.}902$ Note that at the start of the study,

NOTE Confidence: 0.860418372222222

 $00:32:54.910 \dashrightarrow 00:32:59.240$ people averaged about 76 centroids.

NOTE Confidence: 0.860418372222222

 $00:32:59.240 \longrightarrow 00:33:02.480$ Note also that to get into the study,

NOTE Confidence: 0.860418372222222

 $00{:}33{:}02{.}480 \dashrightarrow 00{:}33{:}05{.}390$ the threshold of positivity was

NOTE Confidence: 0.860418372222222

 $00:33:05.390 \longrightarrow 00:33:07.358$ probably about \$0.30 Lloyds.

 $00:33:07.358 \longrightarrow 00:33:10.151$ And then note finally that at the

NOTE Confidence: 0.860418372222222

 $00{:}33{:}10{.}151 \dashrightarrow 00{:}33{:}13{.}157$ end of the study those in the active

NOTE Confidence: 0.860418372222222

00:33:13.157 --> 00:33:15.888 group were at around 23 centroids.

NOTE Confidence: 0.860418372222222

 $00:33:15.890 \rightarrow 00:33:18.176$ Most of them had normal scans,

NOTE Confidence: 0.860418372222222

 $00:33:18.180 \rightarrow 00:33:19.705$ you know, visually and quantitatively

NOTE Confidence: 0.860418372222222

 $00:33:19.705 \longrightarrow 00:33:21.620$ at the end of the study.

NOTE Confidence: 0.860418372222222

 $00{:}33{:}21.620 \dashrightarrow 00{:}33{:}23.104$ And these these differences

NOTE Confidence: 0.860418372222222

00:33:23.104 --> 00:33:24.217 appeared very early,

NOTE Confidence: 0.860418372222222

 $00:33:24.220 \longrightarrow 00:33:25.786$ as early as the very first

NOTE Confidence: 0.860418372222222

 $00:33:25.786 \longrightarrow 00:33:27.310$ pet scan at three months.

NOTE Confidence: 0.82622749111111

00:33:29.840 --> 00:33:30.884 Now moving on,

NOTE Confidence: 0.82622749111111

 $00:33:30.884 \dashrightarrow 00:33:32.972$ you know to other key secondaries,

NOTE Confidence: 0.82622749111111

 $00:33:32.980 \rightarrow 00:33:34.900$ this is the pure cognitive measure,

NOTE Confidence: 0.826227491111111

 $00:33:34.900 \longrightarrow 00:33:39.060$ the 8 US cog which is scored zero to 90.

NOTE Confidence: 0.82622749111111

00:33:39.060 - 00:33:41.820 Higher scores are worse.

NOTE Confidence: 0.82622749111111

 $00:33:41.820 \rightarrow 00:33:45.429$ And what you can see here is that at

 $00:33:45.429 \rightarrow 00:33:49.592$ the end of the 18 months the drug

NOTE Confidence: 0.82622749111111

 $00:33:49.592 \longrightarrow 00:33:52.280$ placebo difference was 1.44 points

NOTE Confidence: 0.82622749111111

 $00:33:52.280 \rightarrow 00:33:55.720$ between drug and placebo, again highly,

NOTE Confidence: 0.82622749111111

 $00:33:55.720 \rightarrow 00:33:58.665$ highly significant representing a 26%.

NOTE Confidence: 0.82622749111111

 $00:33:58.665 \rightarrow 00:34:01.935$ Slowing of decline and and significant

NOTE Confidence: 0.82622749111111

 $00{:}34{:}01{.}935 \dashrightarrow 00{:}34{:}04{.}418$ differences were evident again as

NOTE Confidence: 0.82622749111111

 $00:34:04.418 \rightarrow 00:34:07.099$ early as the six month time point.

NOTE Confidence: 0.82622749111111

 $00:34:07.100 \longrightarrow 00:34:09.907$ And finally, this is the pure functional

NOTE Confidence: 0.82622749111111

 $00{:}34{:}09{.}907 \dashrightarrow 00{:}34{:}11{.}642$ measure relates to activities

NOTE Confidence: 0.82622749111111

00:34:11.642 --> 00:34:15.340 of daily living, the ACS MCIDL.

NOTE Confidence: 0.82622749111111

 $00:34:15.340 \longrightarrow 00:34:17.300$ This is, excuse me,

NOTE Confidence: 0.82622749111111

 $00:34:17.300 \longrightarrow 00:34:20.728$ squared zero to 53.

NOTE Confidence: 0.82622749111111

 $00{:}34{:}20{.}730 \dashrightarrow 00{:}34{:}24{.}545$ In this case lower scores are better.

NOTE Confidence: 0.82622749111111

 $00:34:24.550 \longrightarrow 00:34:26.046$ But we graph it,

NOTE Confidence: 0.826227491111111

 $00{:}34{:}26.046 \dashrightarrow 00{:}34{:}28.918$ you know the same direction for ease

 $00{:}34{:}28{.}918 \dashrightarrow 00{:}34{:}32{.}030$ of understanding and and what you can

NOTE Confidence: 0.82622749111111

 $00:34:32.030 \rightarrow 00:34:35.033$ see is that the placebo group worsens

NOTE Confidence: 0.82622749111111

 $00:34:35.033 \rightarrow 00:34:38.417$ to the tune of about 5 1/2 points.

NOTE Confidence: 0.82622749111111

 $00:34:38.420 \longrightarrow 00:34:41.684$ The actively treated about two points

NOTE Confidence: 0.82622749111111

 $00{:}34{:}41{.}684 \dashrightarrow 00{:}34{:}45{.}159$ less than that highly significant in

NOTE Confidence: 0.82622749111111

 $00{:}34{:}45{.}159 \dashrightarrow 00{:}34{:}49{.}228$ this case representing a 37% slowing of NOTE Confidence: 0.826227491111111

 $00:34:49.228 \longrightarrow 00:34:51.888$ decline with the treatment differences

NOTE Confidence: 0.82622749111111

 $00:34:51.888 \rightarrow 00:34:55.346$ again evident as early as six months.

NOTE Confidence: 0.82622749111111

 $00:34:55.350 \rightarrow 00:34:57.480$ And with regard to clinical meaningfulness,

NOTE Confidence: 0.82622749111111

 $00:34:57.480 \longrightarrow 00:35:00.256$ I would just I find at least in

NOTE Confidence: 0.82622749111111

 $00{:}35{:}00{.}256 \dashrightarrow 00{:}35{:}02{.}997$ in when people see these data,

NOTE Confidence: 0.82622749111111

 $00{:}35{:}03.000 \dashrightarrow 00{:}35{:}05.961$ this is a measure that is more

NOTE Confidence: 0.82622749111111

 $00:35:05.961 \longrightarrow 00:35:08.360$ easily seen as meaningful.

NOTE Confidence: 0.82622749111111

 $00:35:08.360 \longrightarrow 00:35:09.892$ Because of what it is, right?

NOTE Confidence: 0.82622749111111

00:35:09.892 --> 00:35:10.174 Again,

NOTE Confidence: 0.82622749111111

 $00:35:10.174 \rightarrow 00:35:12.430$ these are people who mostly start the study,

 $00:35:12.430 \longrightarrow 00:35:14.902$ able to drive a car, do finances,

NOTE Confidence: 0.82622749111111

 $00{:}35{:}14.902 \dashrightarrow 00{:}35{:}18.340$ you know, Cook, manage their medications.

NOTE Confidence: 0.82622749111111

00:35:18.340 --> 00:35:22.950 And they have, you know, a 37% slowing,

NOTE Confidence: 0.82622749111111

 $00:35:22.950 \longrightarrow 00:35:25.470$ you know, in the loss of such abilities.

NOTE Confidence: 0.826227491111111

00:35:25.470 --> 00:35:26.568 So, you know,

NOTE Confidence: 0.82622749111111

 $00{:}35{:}26.568 \dashrightarrow 00{:}35{:}29.684$ it's hard not to think of such such

NOTE Confidence: 0.82622749111111

 $00:35:29.684 \dashrightarrow 00:35:32.468$ kinds of effects as as meaningful,

NOTE Confidence: 0.82622749111111

 $00:35:32.470 \longrightarrow 00:35:33.540$ you know, in real life.

NOTE Confidence: 0.8465989716666667

00:35:36.820 --> 00:35:38.916 But with regard to clinical meaningfulness, I

NOTE Confidence: 0.8465989716666667

 $00:35:38.916 \rightarrow 00:35:41.600$ want to go on to yet another kind of measure.

NOTE Confidence: 0.8465989716666667

 $00:35:41.600 \rightarrow 00:35:43.368$ Now what I've shown you up until now

NOTE Confidence: 0.846598971666667

 $00{:}35{:}43{.}368 \dashrightarrow 00{:}35{:}45{.}040$ are the top line, you know, results,

NOTE Confidence: 0.8465989716666667

 $00:35:45.040 \rightarrow 00:35:48.680$ you know, the primary and the secondary,

NOTE Confidence: 0.8465989716666667

 $00:35:48.680 \rightarrow 00:35:50.408$ but there are other, you know,

NOTE Confidence: 0.8465989716666667

 $00{:}35{:}50{.}410 \dashrightarrow 00{:}35{:}53{.}164$ more exploratory measures that were done

 $00:35:53.164 \rightarrow 00:35:57.386$ and one of them pertains to quality of life.

NOTE Confidence: 0.8465989716666667

 $00{:}35{:}57{.}390 \dashrightarrow 00{:}35{:}59{.}966$ Quality of life which may not be.

NOTE Confidence: 0.8465989716666667

 $00:35:59.970 \longrightarrow 00:36:03.666$ Fully measured with cognition and function,

NOTE Confidence: 0.8465989716666667

 $00{:}36{:}03{.}670 \dashrightarrow 00{:}36{:}05{.}154$ so in this case.

NOTE Confidence: 0.8465989716666667

 $00{:}36{:}05{.}154 \dashrightarrow 00{:}36{:}07{.}009$ We're looking at four different

NOTE Confidence: 0.846598971666667

 $00{:}36{:}07{.}009 \dashrightarrow 00{:}36{:}09{.}009$ scales that were administered.

NOTE Confidence: 0.846598971666667

 $00:36:09.010 \longrightarrow 00:36:12.258$ The two in the top row are both

NOTE Confidence: 0.8465989716666667

 $00:36:12.258 \rightarrow 00:36:15.423$ assessed quality of life for the

NOTE Confidence: 0.8465989716666667

 $00:36:15.423 \dashrightarrow 00:36:17.124$ patient participant themselves.

NOTE Confidence: 0.8465989716666667

 $00{:}36{:}17.130 \dashrightarrow 00{:}36{:}19.650$ The two in the bottom row of for the,

NOTE Confidence: 0.8465989716666667

 $00:36:19.650 \dashrightarrow 00:36:22.010$ you know the caregiver partner.

NOTE Confidence: 0.8465989716666667

 $00:36:22.010 \longrightarrow 00:36:24.670$ And without going into these in detail

NOTE Confidence: 0.8465989716666667

 $00{:}36{:}24.670 \dashrightarrow 00{:}36{:}27.382$ you know what you can see is that

NOTE Confidence: 0.8465989716666667

 $00:36:27.382 \rightarrow 00:36:29.910$ all four of them show statistically

NOTE Confidence: 0.8465989716666667

 $00:36:29.910 \longrightarrow 00:36:32.856$ significant benefit you know slowing of

NOTE Confidence: 0.8465989716666667

 $00:36:32.856 \rightarrow 00:36:35.149$ decline and and just as a poster child

00:36:35.149 - 00:36:37.768 of these I will cherry pick the QOLA.

NOTE Confidence: 0.8465989716666667

00:36:37.768 --> 00:36:39.322 Be subject because.

NOTE Confidence: 0.8465989716666667

 $00{:}36{:}39{.}322 \dashrightarrow 00{:}36{:}43{.}603$ Here is a a question naire that asked

NOTE Confidence: 0.8465989716666667

 $00:36:43.603 \rightarrow 00:36:46.825$ questions like how happy are you?

NOTE Confidence: 0.8465989716666667

 $00:36:46.830 \rightarrow 00:36:48.986$ How are your relationships with your family,

NOTE Confidence: 0.8465989716666667

 $00:36:48.990 \rightarrow 00:36:49.707$ with your friends?

NOTE Confidence: 0.8465989716666667

00:36:49.707 --> 00:36:51.750 How do you feel about where you're living?

NOTE Confidence: 0.8465989716666667

 $00:36:51.750 \rightarrow 00:36:54.410$ You're you know, your your overall health.

NOTE Confidence: 0.8465989716666667

 $00:36:54.410 \longrightarrow 00:36:56.050$ And on this measure,

NOTE Confidence: 0.8465989716666667

 $00{:}36{:}56{.}050 \dashrightarrow 00{:}36{:}58{.}100$ the Kanab is associated with

NOTE Confidence: 0.8465989716666667

 $00{:}36{:}58{.}100 \dashrightarrow 00{:}36{:}59{.}860$ a 56% lower decline.

NOTE Confidence: 0.846598971666667

 $00{:}36{:}59{.}860 \dashrightarrow 00{:}37{:}02{.}110$ And comparison to the place bo

NOTE Confidence: 0.8465989716666667

 $00:37:02.110 \longrightarrow 00:37:04.746$ group at the end of the study.

NOTE Confidence: 0.8465989716666667

 $00{:}37{:}04.750 \dashrightarrow 00{:}37{:}07.350$ So again for those who think no clinical

NOTE Confidence: 0.8465989716666667

 $00{:}37{:}07{.}350 \dashrightarrow 00{:}37{:}09{.}289$ meaning fulness in these kind of effects,

 $00{:}37{:}09{.}290 \dashrightarrow 00{:}37{:}12{.}093$ I mean I I would I would just ask to to

NOTE Confidence: 0.8465989716666667

 $00{:}37{:}12.093 \dashrightarrow 00{:}37{:}14.424$ look at these these kinds of results.

NOTE Confidence: 0.92799218

 $00{:}37{:}18.290 \dashrightarrow 00{:}37{:}20.215$ Now we're going to talk

NOTE Confidence: 0.92799218

00:37:20.215 --> 00:37:22.340 about safety of like Hannah.

NOTE Confidence: 0.92799218

 $00{:}37{:}22{.}340 \dashrightarrow 00{:}37{:}26{.}316$ And to do that I need to introduce

NOTE Confidence: 0.92799218

 $00:37:26.316 \dashrightarrow 00:37:30.620$ this funny term amyloid related

NOTE Confidence: 0.92799218

00:37:30.620 --> 00:37:33.900 imaging abnormalities shortcut Aria.

NOTE Confidence: 0.92799218

 $00:37:33.900 \longrightarrow 00:37:36.625$ So it's a cute acronym.

NOTE Confidence: 0.92799218

00:37:36.630 --> 00:37:38.268 I personally don't really like it

NOTE Confidence: 0.92799218

 $00{:}37{:}38.268 \dashrightarrow 00{:}37{:}40.249$ a whole lot because it implies that

NOTE Confidence: 0.92799218

 $00:37:40.249 \dashrightarrow 00:37:43.610$ these are only imaging abnormalities,

NOTE Confidence: 0.92799218

 $00{:}37{:}43.610 \dashrightarrow 00{:}37{:}45.410$ you know, whereas they're real pathology.

NOTE Confidence: 0.92799218

 $00:37:45.410 \longrightarrow 00:37:47.178$ So I actually like to use the terms,

NOTE Confidence: 0.92799218

 $00:37:47.180 \longrightarrow 00:37:49.352$ you know, amyloid related,

NOTE Confidence: 0.92799218

 $00{:}37{:}49{.}352 \dashrightarrow 00{:}37{:}51{.}631$ you know, edema and hemosider in.

NOTE Confidence: 0.92799218

 $00:37:51.631 \rightarrow 00:37:54.486$ And I'll slip into those, I'm sure.

- NOTE Confidence: 0.92799218
- $00:37:54.486 \longrightarrow 00:37:57.412$ But in any case, you know,
- NOTE Confidence: 0.92799218
- $00{:}37{:}57{.}412 \dashrightarrow 00{:}38{:}00{.}420$ Aria, there are two types.
- NOTE Confidence: 0.92799218
- $00:38:00.420 \longrightarrow 00:38:04.140$ There's the RE which refused to,
- NOTE Confidence: 0.92799218
- $00:38:04.140 \rightarrow 00:38:08.736$ which refers to effusions or edema,
- NOTE Confidence: 0.92799218
- $00:38:08.740 \longrightarrow 00:38:10.750$ and then there's the RH,
- NOTE Confidence: 0.92799218
- $00{:}38{:}10.750 \dashrightarrow 00{:}38{:}13.642$ which refers to the deposition of
- NOTE Confidence: 0.92799218
- $00:38:13.642 \longrightarrow 00:38:15.570$ the blood product hemosiderin.
- NOTE Confidence: 0.92799218
- $00:38:15.570 \longrightarrow 00:38:18.678$ Aria you seen typically on T2
- NOTE Confidence: 0.92799218
- 00:38:18.678 --> 00:38:22.064 flare sequences on MRI and Aria H $\,$
- NOTE Confidence: 0.92799218
- $00:38:22.064 \rightarrow 00:38:24.349$ on the heme sensitive sequences.
- NOTE Confidence: 0.92799218
- 00:38:24.350 --> 00:38:27.718 Sequences such as, you know, grading, ECHO.
- NOTE Confidence: 0.92799218
- 00:38:27.718 --> 00:38:33.208 Umm or aswi, the so and by the way,
- NOTE Confidence: 0.92799218
- $00:38:33.210 \longrightarrow 00:38:35.730$ why do these occur at all?
- NOTE Confidence: 0.92799218
- $00:38:35.730 \dashrightarrow 00:38:38.278$ It's not fully known but the leading
- NOTE Confidence: 0.92799218
- $00:38:38.278 \rightarrow 00:38:41.090$ view is that monoclonal antibodies,
- NOTE Confidence: 0.92799218

 $00:38:41.090 \rightarrow 00:38:43.220$ anti antibodies by clearing amyloid

NOTE Confidence: 0.92799218

 $00{:}38{:}43.220 \dashrightarrow 00{:}38{:}45.757$ deposits in the blood vessels you

NOTE Confidence: 0.92799218

00:38:45.757 --> 00:38:48.137 know that are in the endothelial wall

NOTE Confidence: 0.92799218

00:38:48.137 --> 00:38:49.828 will cause increased permeability

NOTE Confidence: 0.92799218

 $00:38:49.828 \longrightarrow 00:38:52.168$ of the blood brain barrier,

NOTE Confidence: 0.92799218

 $00:38:52.170 \longrightarrow 00:38:53.382$ which can cause,

NOTE Confidence: 0.92799218

00:38:53.382 --> 00:38:54.190 you know,

NOTE Confidence: 0.92799218

 $00:38:54.190 \dashrightarrow 00:38:56.750$ leakage of molecules that wouldn't

NOTE Confidence: 0.92799218

 $00{:}38{:}56{.}750 \dashrightarrow 00{:}38{:}57{.}774$ normally pass.

NOTE Confidence: 0.92799218

 $00{:}38{:}57{.}780 \dashrightarrow 00{:}38{:}59{.}808$ Drawing fluid osmotically that

NOTE Confidence: 0.92799218

 $00{:}38{:}59{.}808 \dashrightarrow 00{:}39{:}02{.}701$ that's the explanation for edema and

NOTE Confidence: 0.92799218

 $00{:}39{:}02{.}701 \dashrightarrow 00{:}39{:}04{.}807$ then for hemosider in you get actual

NOTE Confidence: 0.92799218

00:39:04.807 --> 00:39:07.440 breakage of of small vessels you know

NOTE Confidence: 0.92799218

 $00:39:07.440 \longrightarrow 00:39:09.702$ with with small bleeds for example.

NOTE Confidence: 0.92799218

 $00{:}39{:}09{.}710 \dashrightarrow 00{:}39{:}12{.}032$ But this slide shows what these

NOTE Confidence: 0.92799218

 $00:39:12.032 \longrightarrow 00:39:14.349$ things look like on MRI scan.

- NOTE Confidence: 0.92799218
- 00:39:14.350 --> 00:39:17.824 So Aria E for edema effusion

00:39:17.824 --> 00:39:22.489 is shown in a C&
amp;D and in a you

NOTE Confidence: 0.92799218

 $00:39:22.489 \longrightarrow 00:39:24.967$ know we're looking at you know

NOTE Confidence: 0.92799218

00:39:24.967 - > 00:39:27.790 the most robust maybe maybe.

NOTE Confidence: 0.92799218

00:39:27.790 --> 00:39:32.746 Obvious example of you know a parenchymal

NOTE Confidence: 0.92799218

 $00:39:32.746 \rightarrow 00:39:36.780$ signal abnormality here in the right

NOTE Confidence: 0.92799218

 $00:39:36.780 \rightarrow 00:39:42.570$ occipital lobe with some gyral swelling.

NOTE Confidence: 0.92799218

00:39:42.570 --> 00:39:43.682 In C,

NOTE Confidence: 0.92799218

 $00{:}39{:}43.682 \dashrightarrow 00{:}39{:}48.130$ we're looking at a more pure sulcal effusion,

NOTE Confidence: 0.92799218

 $00:39:48.130 \rightarrow 00:39:50.346$ which is another way that this can present

NOTE Confidence: 0.92799218

 $00:39:50.346 \rightarrow 00:39:52.610$ not so much parenchymal as you know,

NOTE Confidence: 0.92799218

 $00:39:52.610 \longrightarrow 00:39:53.549$ a sulcal effusion.

NOTE Confidence: 0.92799218

 $00{:}39{:}53{.}549 \dashrightarrow 00{:}39{:}55{.}740$ And then in D we're looking at

NOTE Confidence: 0.92799218

 $00{:}39{:}55{.}813 \dashrightarrow 00{:}39{:}57{.}669$ A at A at a very subtle case,

NOTE Confidence: 0.92799218

00:39:57.670 - 00:40:02.450 which we do see where just a wee bit of,

00:40:02.450 --> 00:40:02.980 you know,

NOTE Confidence: 0.92799218

 $00{:}40{:}02{.}980 \dashrightarrow 00{:}40{:}04{.}835$ gyral swelling is evident and a little

NOTE Confidence: 0.92799218

 $00{:}40{:}04{.}835 \dashrightarrow 00{:}40{:}06{.}835$ bit of a circle effusion is evidence.

NOTE Confidence: 0.92799218

 $00{:}40{:}06{.}840 \dashrightarrow 00{:}40{:}10{.}064$ So that would be a very subtle case

NOTE Confidence: 0.92799218

 $00{:}40{:}10.064 \dashrightarrow 00{:}40{:}12.938$ with regard to Aria H as we'll see.

NOTE Confidence: 0.92799218

 $00{:}40{:}12.940 \dashrightarrow 00{:}40{:}14.980$ This can come in different forms.

NOTE Confidence: 0.92799218

 $00:40:14.980 \longrightarrow 00:40:17.506$ The one shown here is microhemorrhages

NOTE Confidence: 0.92799218

 $00{:}40{:}17.506 \dashrightarrow 00{:}40{:}20.577$ and that's in panel B in the red

NOTE Confidence: 0.92799218

 $00{:}40{:}20.577 \dashrightarrow 00{:}40{:}22.539$ circle you see these three dots.

NOTE Confidence: 0.92799218

 $00:40:22.540 \longrightarrow 00:40:23.880$ Micro hemorrhages are defined

NOTE Confidence: 0.92799218

 $00{:}40{:}23.880 \dashrightarrow 00{:}40{:}25.555$ as less than a centimeter.

NOTE Confidence: 0.92799218

 $00:40:25.560 \rightarrow 00:40:27.090$ These are much smaller than that,

NOTE Confidence: 0.92799218

00:40:27.090 --> 00:40:28.370 you know, maybe 3 millimeters.

NOTE Confidence: 0.92799218

 $00{:}40{:}28.370 \dashrightarrow 00{:}40{:}32.234$ So they tend to occur where edema

NOTE Confidence: 0.92799218

 $00:40:32.234 \longrightarrow 00:40:35.198$ has also occurred by the way.

NOTE Confidence: 0.92799218

 $00:40:35.200 \longrightarrow 00:40:37.396$ And we'll talk more about that.

 $00:40:37.400 \longrightarrow 00:40:40.200$ The the other forms of RH not shown

NOTE Confidence: 0.92799218

 $00{:}40{:}40{.}200 \dashrightarrow 00{:}40{:}43{.}032$ here are superficial side rosis and

NOTE Confidence: 0.92799218

00:40:43.032 - 00:40:45.576 macro hemorrhage, which is you know,

NOTE Confidence: 0.92799218

 $00{:}40{:}45{.}576 \dashrightarrow 00{:}40{:}47{.}845$ to find us more than a centimeter

NOTE Confidence: 0.92799218

 $00:40:47.845 \longrightarrow 00:40:50.425$ and we'll talk more about that.

NOTE Confidence: 0.92799218

 $00{:}40{:}50{.}430 \dashrightarrow 00{:}40{:}53{.}321$ So now going back to the safety

NOTE Confidence: 0.92799218

 $00:40:53.321 \longrightarrow 00:40:56.097$ data for Liquin amab in light of

NOTE Confidence: 0.92799218

 $00:40:56.097 \longrightarrow 00:40:58.900$ in light of that first of all

NOTE Confidence: 0.92799218

 $00{:}40{:}58{.}900 \dashrightarrow 00{:}41{:}00{.}700$ here we're looking at.

NOTE Confidence: 0.6871895

 $00:41:00.700 \rightarrow 00:41:05.442$ The. We're looking at the the most

NOTE Confidence: 0.6871895

 $00{:}41{:}05{.}442 \dashrightarrow 00{:}41{:}07{.}360$ serious adverse events that occur.

NOTE Confidence: 0.6871895

 $00{:}41{:}07{.}360 \dashrightarrow 00{:}41{:}10{.}018$ So for example, you know deaths,

NOTE Confidence: 0.6871895

 $00{:}41{:}10.018 \dashrightarrow 00{:}41{:}13.560$ deaths were fairly balanced 7 on placebo,

NOTE Confidence: 0.6871895

 $00{:}41{:}13.560 \dashrightarrow 00{:}41{:}15.152$ 6 on the Kanab.

NOTE Confidence: 0.6871895

 $00:41:15.152 \rightarrow 00:41:18.220$ Next we look at serious adverse events,

 $00:41:18.220 \rightarrow 00:41:20.245$ things that require for example

NOTE Confidence: 0.6871895

00:41:20.245 --> 00:41:22.270 hospitalization and what I

NOTE Confidence: 0.6871895

 $00{:}41{:}22{.}341 \dashrightarrow 00{:}41{:}24{.}493$ want you to see here is that the,

NOTE Confidence: 0.6871895

 $00:41:24.500 \rightarrow 00:41:26.315$ it's really only three kinds

NOTE Confidence: 0.6871895

 $00:41:26.315 \longrightarrow 00:41:28.130$ of events that are occurring

NOTE Confidence: 0.6871895

 $00{:}41{:}28{.}202 \dashrightarrow 00{:}41{:}30{.}176$ more on the Kanab than placebo,

NOTE Confidence: 0.6871895

 $00{:}41{:}30{.}180 \dashrightarrow 00{:}41{:}32{.}390$ it's those that are associated

NOTE Confidence: 0.6871895

 $00:41:32.390 \longrightarrow 00:41:33.667$ with these RERH.

NOTE Confidence: 0.6871895

 $00{:}41{:}33.667 \dashrightarrow 00{:}41{:}35.989$ And then the third category would

NOTE Confidence: 0.6871895

 $00:41:35.989 \longrightarrow 00:41:37.880$ be infusion related reactions,

NOTE Confidence: 0.6871895

 $00:41:37.880 \longrightarrow 00:41:41.330$ you know mild hypersensitivity reactions.

NOTE Confidence: 0.6871895

 $00{:}41{:}41{.}330 \dashrightarrow 00{:}41{:}44{.}108$ All other SME's are actually you

NOTE Confidence: 0.6871895

 $00{:}41{:}44.108 \dashrightarrow 00{:}41{:}46.770$ know quite balanced between drug and

NOTE Confidence: 0.6871895

 $00:41:46.770 \longrightarrow 00:41:49.311$ placebo and and again as much as

NOTE Confidence: 0.6871895

 $00:41:49.311 \rightarrow 00:41:52.148$ these essays are more common on drug,

NOTE Confidence: 0.6871895

 $00:41:52.150 \rightarrow 00:41:54.046$ they're they're still not very common.

- NOTE Confidence: 0.6871895
- $00:41:54.050 \longrightarrow 00:41:55.807$ I mean they're all in the order

 $00:41:55.807 \rightarrow 00:41:56.970$ of 1% frequency.

NOTE Confidence: 0.877360036

 $00:41:59.460 \rightarrow 00:42:03.023$ This slide shows you know common adverse

NOTE Confidence: 0.877360036

 $00:42:03.023 \rightarrow 00:42:05.939$ events now including non serious adverse

NOTE Confidence: 0.877360036

 $00{:}42{:}05{.}939 \dashrightarrow 00{:}42{:}09{.}462$ events and and again I think the the

NOTE Confidence: 0.877360036

 $00{:}42{:}09{.}462 \dashrightarrow 00{:}42{:}12{.}662$ real take home message is that it's the

NOTE Confidence: 0.877360036

 $00:42:12.662 \longrightarrow 00:42:15.440$ it's the ones in these three categories

NOTE Confidence: 0.877360036

 $00{:}42{:}15{.}440 \dashrightarrow 00{:}42{:}18{.}596$ even for non serious AE that are more

NOTE Confidence: 0.877360036

00:42:18.596 --> 00:42:20.840 more common on lecanu amab infusion

NOTE Confidence: 0.877360036

 $00{:}42{:}20{.}914 \dashrightarrow 00{:}42{:}23{.}034$ related reactions RER AH everything

NOTE Confidence: 0.877360036

 $00{:}42{:}23.034 \dashrightarrow 00{:}42{:}26.092$ else down at the bottom of the slide is

NOTE Confidence: 0.877360036

 $00:42:26.092 \rightarrow 00:42:28.570$ is not is really not more common on Lebanon.

NOTE Confidence: 0.877360036

 $00:42:28.570 \longrightarrow 00:42:30.826$ So want to just take a moment to

NOTE Confidence: 0.877360036

 $00{:}42{:}30{.}826 \dashrightarrow 00{:}42{:}32{.}821$ focus on infusion related reactions

NOTE Confidence: 0.877360036

 $00{:}42{:}32{.}821 \dashrightarrow 00{:}42{:}35{.}999$ because I won't talk about these again.

 $00:42:36.000 \longrightarrow 00:42:40.292$ So 26.4% with like Kanab,

NOTE Confidence: 0.877360036

 $00{:}42{:}40{.}292 \dashrightarrow 00{:}42{:}42{.}272$ 7.4% with placebo.

NOTE Confidence: 0.877360036

 $00:42:42.272 \longrightarrow 00:42:45.732$ These tend to be almost always

NOTE Confidence: 0.877360036

 $00:42:45.732 \longrightarrow 00:42:47.160$ mild to moderate,

NOTE Confidence: 0.877360036

 $00{:}42{:}47{.}160 \dashrightarrow 00{:}42{:}49{.}383$ you know 96% of them are they tend to

NOTE Confidence: 0.877360036

 $00:42:49.383 \rightarrow 00:42:51.357$ occur with the very first infusion,

NOTE Confidence: 0.877360036

 $00:42:51.360 \rightarrow 00:42:53.370$ most commonly the only occur once.

NOTE Confidence: 0.7749822

00:42:55.660 --> 00:42:59.070 And RE&RHM going to talk about

NOTE Confidence: 0.7749822

 $00{:}42{:}59{.}070 \dashrightarrow 00{:}43{:}01{.}282$ in the next slide, next slides.

NOTE Confidence: 0.7749822

00:43:01.282 --> 00:43:04.978 So, so Ari E you know many of

NOTE Confidence: 0.7749822

 $00{:}43{:}04{.}978 \dashrightarrow 00{:}43{:}07{.}532$ us think this is really the most

NOTE Confidence: 0.7749822

 $00:43:07.532 \longrightarrow 00:43:09.777$ important toxicity of these

NOTE Confidence: 0.7749822

00:43:09.777 --> 00:43:12.830 drugs because it is not rare,

NOTE Confidence: 0.7749822

00:43:12.830 - > 00:43:15.500 it is sometimes symptomatic and

NOTE Confidence: 0.7749822

 $00{:}43{:}15{.}500 \dashrightarrow 00{:}43{:}18{.}170$ and necessitates you know pausing

NOTE Confidence: 0.7749822

 $00:43:18.257 \rightarrow 00:43:22.410$ infusions until it resolves. Um.

- NOTE Confidence: 0.7749822
- $00{:}43{:}22{.}410 \dashrightarrow 00{:}43{:}26{.}146$ So the the key statistic here that you

 $00:43:26.146 \rightarrow 00:43:30.038$ can see is 12.6% frequency on LEINAD,

NOTE Confidence: 0.7749822

 $00{:}43{:}30{.}038 \dashrightarrow 00{:}43{:}31{.}270$ 1.7 on placebo.

NOTE Confidence: 0.7749822

 $00:43:31.270 \rightarrow 00:43:33.550$ You know why does it occur on placebo?

NOTE Confidence: 0.7749822

 $00:43:33.550 \longrightarrow 00:43:36.502$ Well it it does occur spontaneously

NOTE Confidence: 0.7749822

 $00:43:36.502 \rightarrow 00:43:39.510$ in related to amyloid angiopathy.

NOTE Confidence: 0.7749822

 $00{:}43{:}39{.}510 \dashrightarrow 00{:}43{:}42{.}147$ You know CIA people with a lot of of

NOTE Confidence: 0.7749822

 $00:43:42.147 \rightarrow 00:43:43.710$ amyloid angiopathy are disqualified

NOTE Confidence: 0.7749822

 $00:43:43.710 \longrightarrow 00:43:46.510$ from the study in the 1st place.

NOTE Confidence: 0.7749822

 $00{:}43{:}46{.}510 \dashrightarrow 00{:}43{:}48{.}463$ You know if they have more than

NOTE Confidence: 0.7749822

 $00:43:48.463 \longrightarrow 00:43:49.599$ four microhemorrhages at the

NOTE Confidence: 0.7749822

 $00:43:49.599 \longrightarrow 00:43:51.063$ start they they don't enroll in

NOTE Confidence: 0.7749822

 $00{:}43{:}51.063 \dashrightarrow 00{:}43{:}52.599$ the study for safety reasons.

NOTE Confidence: 0.7749822

 $00{:}43{:}52.600 \dashrightarrow 00{:}43{:}55.328$ But there can be spontaneous cases of this.

NOTE Confidence: 0.832082954

 $00:43:57.360 \longrightarrow 00:44:01.418$ And. Symptomatic cases are only 2.8%,

- $00:44:01.418 \longrightarrow 00:44:03.626$ you know, of, of the total.
- NOTE Confidence: 0.832082954
- 00:44:03.630 00:44:04.731 When they're symptomatic,
- NOTE Confidence: 0.832082954
- $00:44:04.731 \rightarrow 00:44:06.566$ what are the symptoms usually,
- NOTE Confidence: 0.832082954
- 00:44:06.570 --> 00:44:08.650 you know, headache, visual blurring,
- NOTE Confidence: 0.832082954
- $00:44:08.650 \longrightarrow 00:44:10.170$ confusion, things like that.
- NOTE Confidence: 0.832082954
- $00:44:10.170 \longrightarrow 00:44:12.960$ And and you know and in general
- NOTE Confidence: 0.832082954
- $00:44:12.960 \rightarrow 00:44:15.970$ working with a lot of these antibodies,
- NOTE Confidence: 0.832082954
- 00:44:15.970 --> 00:44:17.078 I mean, you know,
- NOTE Confidence: 0.832082954
- $00:44:17.078 \rightarrow 00:44:19.250$ I view these as very manageable numbers.
- NOTE Confidence: 0.832082954
- $00:44:19.250 \longrightarrow 00:44:21.077$ I mean I will tell you that
- NOTE Confidence: 0.832082954
- $00:44:21.077 \rightarrow 00:44:23.511$ they're 1/2 to 1/3 of the rate of
- NOTE Confidence: 0.832082954
- 00:44:23.511 -> 00:44:25.096 what other trials have reported,
- NOTE Confidence: 0.832082954
- 00:44:25.100 -> 00:44:26.680 you know, with other antibodies
- NOTE Confidence: 0.832082954
- 00:44:26.680 --> 00:44:27.944 without going into detail,
- NOTE Confidence: 0.832082954
- $00:44:27.950 \longrightarrow 00:44:29.552$ not head-to-head comparisons.
- NOTE Confidence: 0.832082954
- 00:44:29.552 --> 00:44:32.400 Or just, you know, just lower,

- NOTE Confidence: 0.832082954
- $00:44:32.400 \longrightarrow 00:44:34.180$ these are substantially lower

 $00{:}44{:}34{.}180 \dashrightarrow 00{:}44{:}36{.}820$ numbers than the other trials report.

NOTE Confidence: 0.721029231153846

 $00{:}44{:}41.850 \dashrightarrow 00{:}44{:}44.762$ Now a little more detail on Aria H

NOTE Confidence: 0.721029231153846

 $00:44:44.762 \rightarrow 00:44:47.589$ Again refers to hemosiderin deposition.

NOTE Confidence: 0.798711484545454

00:44:49.820 --> 00:44:51.086 Hemosiderin, you know,

NOTE Confidence: 0.798711484545454

 $00:44:51.086 \longrightarrow 00:44:54.430$ a blood product that shows up on the.

NOTE Confidence: 0.798711484545454

 $00{:}44{:}54{.}430 \dashrightarrow 00{:}44{:}58{.}100$ Team sensitive sequences on MRI.

NOTE Confidence: 0.798711484545454

00:44:58.100 --> 00:45:00.510 So just to review again, Aria,

NOTE Confidence: 0.798711484545454

 $00:45:00.510 \longrightarrow 00:45:02.510$ Ah, you know is generally

NOTE Confidence: 0.798711484545454

 $00:45:02.510 \longrightarrow 00:45:04.110$ comes in three categories,

NOTE Confidence: 0.798711484545454

 $00:45:04.110 \longrightarrow 00:45:05.154$ microhemorrhages that we

NOTE Confidence: 0.798711484545454

 $00{:}45{:}05{.}154 \dashrightarrow 00{:}45{:}07{.}242$ saw on the on the image,

NOTE Confidence: 0.798711484545454

 $00{:}45{:}07.250 \dashrightarrow 00{:}45{:}09.780$ they're less than a centimeter.

NOTE Confidence: 0.798711484545454

00:45:09.780 --> 00:45:13.224 Superficial side rosis is a you know is

NOTE Confidence: 0.798711484545454

 $00{:}45{:}13.224 \dashrightarrow 00{:}45{:}17.165$ a thin deposition of hemosider in on the

 $00:45:17.165 \rightarrow 00:45:21.650$ brain surface actually in the sub peel space.

NOTE Confidence: 0.798711484545454

 $00{:}45{:}21.650 \dashrightarrow 00{:}45{:}23.800$ And um, cerebral macro hemorrhage

NOTE Confidence: 0.798711484545454

00:45:23.800 --> 00:45:27.509 is you know is a micro hemorrhage.

NOTE Confidence: 0.798711484545454

 $00:45:27.510 \rightarrow 00:45:30.030$ Well it's more than a centimeter you know

NOTE Confidence: 0.798711484545454

 $00{:}45{:}30{.}030 \dashrightarrow 00{:}45{:}32{.}709$ it's it's the delineation between the two.

NOTE Confidence: 0.798711484545454

 $00:45:32.710 \rightarrow 00:45:35.294$ So what you can see overall here is

NOTE Confidence: 0.798711484545454

 $00:45:35.294 \longrightarrow 00:45:38.490$ that the the key statistic is that 17.3

NOTE Confidence: 0.798711484545454

00:45:38.490 --> 00:45:43.452 frequency for RH with Lacan Amab 9.0 placebo.

NOTE Confidence: 0.798711484545454

 $00{:}45{:}43{.}452 \dashrightarrow 00{:}45{:}47{.}940$ Of real note though is that the increase

NOTE Confidence: 0.798711484545454

 $00:45:48.048 \rightarrow 00:45:51.976$ in like cannab is really area and the.

NOTE Confidence: 0.798711484545454

 $00{:}45{:}51{.}976 \dashrightarrow 00{:}45{:}53{.}824$ Actually micro hemorrhages that

NOTE Confidence: 0.798711484545454

 $00{:}45{:}53.824 \dashrightarrow 00{:}45{:}55.710$ are associated with edema.

NOTE Confidence: 0.798711484545454

 $00:45:55.710 \rightarrow 00:45:59.166$ So if you take cases where there's no edema,

NOTE Confidence: 0.798711484545454

 $00:45:59.170 \rightarrow 00:46:01.135$ these actually aren't more common

NOTE Confidence: 0.798711484545454

 $00:46:01.135 \longrightarrow 00:46:02.707$ on drug than placebo.

NOTE Confidence: 0.798711484545454

 $00:46:02.710 \longrightarrow 00:46:05.302$ And again they have for a lot of

- NOTE Confidence: 0.798711484545454
- $00{:}46{:}05{.}302 \dashrightarrow 00{:}46{:}06{.}841$ these occurred spontaneously again
- NOTE Confidence: 0.798711484545454
- 00:46:06.841 --> 00:46:09.690 in relation to you know mild CAA,
- NOTE Confidence: 0.798711484545454
- $00:46:09.690 \longrightarrow 00:46:11.560$ you know in these subjects.
- NOTE Confidence: 0.647796774
- $00{:}46{:}13.610$ --> $00{:}46{:}18.348$ And RH is almost always asymptomatic.
- NOTE Confidence: 0.647796774
- 00:46:18.348 --> 00:46:20.820 It when it's symptomatic,
- NOTE Confidence: 0.647796774
- 00:46:20.820 --> 00:46:23.238 it's usually because it's with RE,
- NOTE Confidence: 0.647796774
- $00:46:23.240 \longrightarrow 00:46:26.196$ and it also is some, you know,
- NOTE Confidence: 0.647796774
- $00:46:26.196 \longrightarrow 00:46:30.120$ a boy for genotype is a risk for RH.
- NOTE Confidence: 0.647796774
- 00:46:30.120 --> 00:46:32.031 Now I wanna spend a little bit
- NOTE Confidence: 0.647796774
- 00:46:32.031 --> 00:46:34.120 of time on macro hemorrhages,
- NOTE Confidence: 0.647796774
- $00:46:34.120 \rightarrow 00:46:37.395$ which have caught a lot of press,
- NOTE Confidence: 0.647796774
- $00:46:37.395 \longrightarrow 00:46:39.300$ especially, you know,
- NOTE Confidence: 0.647796774
- $00:46:39.300 \longrightarrow 00:46:42.923$ large low bar and fatal hemorrhages.
- NOTE Confidence: 0.647796774
- 00:46:42.923 --> 00:46:45.138 And I think that they,
- NOTE Confidence: 0.647796774
- $00:46:45.140 \longrightarrow 00:46:46.190$ as important as they are,
- NOTE Confidence: 0.647796774

 $00:46:46.190 \longrightarrow 00:46:49.130$ I think they've gotten a real inordinate

NOTE Confidence: 0.647796774

 $00:46:49.130 \rightarrow 00:46:52.000$ and very imbalanced coverage in the press.

NOTE Confidence: 0.647796774

 $00:46:52.000 \longrightarrow 00:46:55.516$ So, so just to be clear.

NOTE Confidence: 0.647796774

 $00:46:55.520 \longrightarrow 00:46:58.044$ In the double-blind study,

NOTE Confidence: 0.647796774

 $00{:}46{:}58.044 \dashrightarrow 00{:}47{:}01.287$ there was one fat al lobar hemorrhage,

NOTE Confidence: 0.647796774

 $00{:}47{:}01.287 \dashrightarrow 00{:}47{:}04.430$ and it occurred in the placebo group.

NOTE Confidence: 0.647796774

 $00{:}47{:}04{.}430 \dashrightarrow 00{:}47{:}06{.}878$ The two that have been reported in the

NOTE Confidence: 0.647796774

 $00{:}47{:}06.878 \dashrightarrow 00{:}47{:}09.346$ press are in the open label extension.

NOTE Confidence: 0.647796774

00:47:09.350 --> 00:47:09.960 You know,

NOTE Confidence: 0.647796774

 $00:47:09.960 \longrightarrow 00:47:13.080$ one of these was a 65 year old

NOTE Confidence: 0.647796774

00:47:13.080 --> 00:47:16.260 woman E4 homozygote who had a

NOTE Confidence: 0.647796774

 $00{:}47{:}16.260 \dashrightarrow 00{:}47{:}20.537$ left MCA stroke occlusion and was

NOTE Confidence: 0.647796774

 $00{:}47{:}20.537 \dashrightarrow 00{:}47{:}24.630$ administered TPA emergently in the ER.

NOTE Confidence: 0.647796774

 $00{:}47{:}24.630 \dashrightarrow 00{:}47{:}27.073$ And those of you familiar know that

NOTE Confidence: 0.647796774

 $00{:}47{:}27.073 \dashrightarrow 00{:}47{:}29.300$ there's a there's a substantial risk

NOTE Confidence: 0.647796774

 $00:47:29.300 \rightarrow 00:47:31.883$ of major hemorrhage with with TPA and
- NOTE Confidence: 0.647796774
- $00:47:31.953 \rightarrow 00:47:34.459$ that's what happened and she died.
- NOTE Confidence: 0.647796774
- $00{:}47{:}34{.}460 \dashrightarrow 00{:}47{:}37{.}612$ The second case is of a A a
- NOTE Confidence: 0.647796774
- $00:47:37.612 \longrightarrow 00:47:40.078$ fairly frail 87 year old man.
- NOTE Confidence: 0.647796774
- $00{:}47{:}40.080 \dashrightarrow 00{:}47{:}41.070$ He's actually older than would
- NOTE Confidence: 0.647796774
- $00:47:41.070 \longrightarrow 00:47:42.320$ have been allowed in the study.
- NOTE Confidence: 0.647796774
- $00:47:42.320 \longrightarrow 00:47:45.006$ At the start of the study E4 non
- NOTE Confidence: 0.647796774
- $00{:}47{:}45.006 \dashrightarrow 00{:}47{:}47.364$ carrier who was on the anticoagulant
- NOTE Confidence: 0.647796774
- 00:47:47.364 --> 00:47:49.979 pick Saban for atrial fibrillation,
- NOTE Confidence: 0.647796774
- $00{:}47{:}49{.}980 \dashrightarrow 00{:}47{:}52{.}108$ he had a lobar hemorrhage and and
- NOTE Confidence: 0.647796774
- $00:47:52.108 \longrightarrow 00:47:53.800$ thus the apixaban was stopped.
- NOTE Confidence: 0.647796774
- 00:47:53.800 00:47:55.735 But then now with untreated
- NOTE Confidence: 0.647796774
- $00:47:55.735 \longrightarrow 00:47:56.509$ atrial fibrillation,
- NOTE Confidence: 0.647796774
- $00{:}47{:}56{.}510 \dashrightarrow 00{:}47{:}58{.}946$ he had an MRI and which is
- NOTE Confidence: 0.647796774
- $00{:}47{:}58{.}946 \dashrightarrow 00{:}48{:}00{.}879$ probably what he died from.
- NOTE Confidence: 0.647796774
- $00:48:00.880 \longrightarrow 00:48:02.014$ So you know,
- NOTE Confidence: 0.647796774

 $00:48:02.014 \rightarrow 00:48:04.660$ are these cases related to the kanima?

NOTE Confidence: 0.647796774

00:48:04.660 --> 00:48:07.284 You know, I would say possibly they are.

NOTE Confidence: 0.647796774

 $00:48:07.290 \longrightarrow 00:48:08.702$ On the other hand,

NOTE Confidence: 0.647796774

00:48:08.702 --> 00:48:10.467 as a blinded site investigator,

NOTE Confidence: 0.647796774

 $00{:}48{:}10{.}470 \dashrightarrow 00{:}48{:}13{.}454$ I would have said that the case on

NOTE Confidence: 0.647796774

 $00:48:13.454 \rightarrow 00:48:16.069$ placebo was also possibly related.

NOTE Confidence: 0.647796774

00:48:16.070 - 00:48:18.625 So you know, we really don't know.

NOTE Confidence: 0.647796774

 $00:48:18.630 \longrightarrow 00:48:21.752$ And if you look at the overall

NOTE Confidence: 0.647796774

 $00{:}48{:}21.752 \dashrightarrow 00{:}48{:}24.051$ frequency of these cases, it's,

NOTE Confidence: 0.647796774

 $00:48:24.051 \rightarrow 00:48:26.178$ it's about one in 1000, right,

NOTE Confidence: 0.647796774

 $00:48:26.178 \longrightarrow 00:48:29.286$ it's 0.1% for people taking placebo.

NOTE Confidence: 0.647796774

 $00:48:29.290 \rightarrow 00:48:31.498$ It's about 0.1% for people taking

NOTE Confidence: 0.647796774

00:48:31.498 --> 00:48:33.496 like canama when you consider

NOTE Confidence: 0.647796774

 $00:48:33.496 \longrightarrow 00:48:35.766$ the greater exposure to lucama.

NOTE Confidence: 0.647796774

 $00:48:35.770 \longrightarrow 00:48:38.040$ On the open label extension.

NOTE Confidence: 0.647796774

 $00:48:38.040 \longrightarrow 00:48:39.496$ So I think we need to balance

 $00:48:39.496 \longrightarrow 00:48:41.101$ you know what we hear in the

NOTE Confidence: 0.647796774

 $00:48:41.101 \rightarrow 00:48:42.493$ press with some of these numbers.

NOTE Confidence: 0.647796774

 $00:48:42.500 \rightarrow 00:48:44.999$ And I especially think we need to

NOTE Confidence: 0.647796774

00:48:44.999 --> 00:48:48.012 balance this issue which is that there

NOTE Confidence: 0.647796774

 $00:48:48.012 \rightarrow 00:48:50.640$ can be catastrophic events like this,

NOTE Confidence: 0.647796774

 $00{:}48{:}50{.}640 \dashrightarrow 00{:}48{:}52{.}670$ balance that against the untreated

NOTE Confidence: 0.647796774

00:48:52.670 --> 00:48:54.294 state of Alzheimer's disease,

NOTE Confidence: 0.647796774

00:48:54.300 - 00:48:57.316 which is uniformly progressive

NOTE Confidence: 0.647796774

 $00:48:57.316 \longrightarrow 00:48:59.578$ and uniformly fatal.

NOTE Confidence: 0.647796774

 $00{:}48{:}59{.}580 \dashrightarrow 00{:}49{:}01{.}788$ And in fact when we talk to patients

NOTE Confidence: 0.647796774

 $00:49:01.788 \longrightarrow 00:49:03.480$ and their families about these

NOTE Confidence: 0.647796774

 $00{:}49{:}03{.}480 \dashrightarrow 00{:}49{:}05{.}640$ risks in relation to these drugs,

NOTE Confidence: 0.647796774

 $00:49:05.640 \longrightarrow 00:49:06.930$ people who are interested in

NOTE Confidence: 0.647796774

 $00:49:06.930 \longrightarrow 00:49:08.220$ these drugs to begin with.

NOTE Confidence: 0.647796774

 $00:49:08.220 \rightarrow 00:49:10.068$ Which are the people I talked to?

 $00:49:10.070 \longrightarrow 00:49:12.650$ It's you really don't hear

NOTE Confidence: 0.647796774

 $00:49:12.650 \longrightarrow 00:49:15.230$ people being deterred by these,

NOTE Confidence: 0.647796774

00:49:15.230 --> 00:49:19.106 you know, this degree of risk.

NOTE Confidence: 0.647796774

 $00{:}49{:}19{.}110 \dashrightarrow 00{:}49{:}23{.}107$ Now I want to finish with biomarkers

NOTE Confidence: 0.647796774

 $00{:}49{:}23.110 \dashrightarrow 00{:}49{:}25.050$ because I think the biomarker

NOTE Confidence: 0.647796774

00:49:25.050 - 00:49:26.990 results are are probably every

NOTE Confidence: 0.647796774

 $00:49:27.057 \longrightarrow 00:49:28.821$ bit as interesting as the as

NOTE Confidence: 0.647796774

 $00{:}49{:}28.821 \dashrightarrow 00{:}49{:}30.536$ the you know clinical effects.

NOTE Confidence: 0.647796774

 $00{:}49{:}30{.}536 \dashrightarrow 00{:}49{:}33{.}840$ By way of background when we talk about

NOTE Confidence: 0.647796774

 $00{:}49{:}33{.}913 \dashrightarrow 00{:}49{:}36{.}449$ biomarkers and Alzheimer's disease,

NOTE Confidence: 0.647796774

 $00{:}49{:}36{.}450 \dashrightarrow 00{:}49{:}38{.}916$ I want to introduce the the

NOTE Confidence: 0.647796774

 $00{:}49{:}38{.}916 \dashrightarrow 00{:}49{:}41{.}450$ current notion of of Alzheimer's

NOTE Confidence: 0.647796774

 $00:49:41.450 \longrightarrow 00:49:43.570$ you know biologically which is

NOTE Confidence: 0.591725844285714

00:49:43.570 --> 00:49:46.846 this a TN classification, a for amyloid,

NOTE Confidence: 0.591725844285714

 $00:49:46.850 \dashrightarrow 00:49:50.666$ T for tile and for neurodegeneration.

NOTE Confidence: 0.591725844285714

 $00:49:50.670 \rightarrow 00:49:53.316$ So most people with Alzheimer's disease,

- NOTE Confidence: 0.591725844285714
- $00:49:53.320 \longrightarrow 00:49:55.532$ you know, start out in the yellow
- NOTE Confidence: 0.591725844285714
- $00:49:55.532 \rightarrow 00:49:57.600$ circle that is amyloid doesn't.
- NOTE Confidence: 0.591725844285714
- $00:49:57.600 \rightarrow 00:50:00.316$ And what that means is the amyloid
- NOTE Confidence: 0.591725844285714
- $00:50:00.316 \rightarrow 00:50:02.800$ pathogenesis tends to be detected first.
- NOTE Confidence: 0.591725844285714
- 00:50:02.800 00:50:06.100 From there, if they have Alzheimer's,
- NOTE Confidence: 0.591725844285714
- $00:50:06.100 \longrightarrow 00:50:07.564$ eventually Tau pathology
- NOTE Confidence: 0.591725844285714
- $00:50:07.564 \longrightarrow 00:50:09.516$ will also be detectable.
- NOTE Confidence: 0.591725844285714
- $00:50:09.520 \longrightarrow 00:50:10.860$ It may be there earlier,
- NOTE Confidence: 0.591725844285714
- $00:50:10.860 \longrightarrow 00:50:12.420$ but the ways it's detected,
- NOTE Confidence: 0.591725844285714
- $00:50:12.420 \longrightarrow 00:50:14.340$ you know, tend to to follow.
- NOTE Confidence: 0.591725844285714
- $00:50:14.340 \rightarrow 00:50:17.034$ And important thing is that Alzheimer's
- NOTE Confidence: 0.591725844285714
- $00:50:17.034 \dashrightarrow 00:50:21.162$ just defined by this intersection, A plus.
- NOTE Confidence: 0.591725844285714
- $00{:}50{:}21.162 \dashrightarrow 00{:}50{:}24.367$ Key is equals Alzheimer's disease.
- NOTE Confidence: 0.591725844285714
- $00{:}50{:}24.370 \dashrightarrow 00{:}50{:}27.298$ These people also will will progress
- NOTE Confidence: 0.591725844285714
- $00{:}50{:}27{.}298 \dashrightarrow 00{:}50{:}29{.}726$ to have neurodegeneration the blue
- NOTE Confidence: 0.591725844285714

 $00:50:29.726 \longrightarrow 00:50:32.120$ circle and then there's the green

NOTE Confidence: 0.591725844285714

 $00{:}50{:}32.120 \dashrightarrow 00{:}50{:}34.950$ circle which is cognitive impairment.

NOTE Confidence: 0.591725844285714

 $00:50:34.950 \longrightarrow 00:50:37.337$ And important to point out that people NOTE Confidence: 0.591725844285714

 $00:50:37.337 \longrightarrow 00:50:40.692$ kind of can have all of these pathologies

NOTE Confidence: 0.591725844285714

 $00:50:40.692 \rightarrow 00:50:42.947$ and still remain cognitively normal.

NOTE Confidence: 0.591725844285714

 $00{:}50{:}42{.}950 \dashrightarrow 00{:}50{:}45{.}421$ And it's the people are cognitively normal NOTE Confidence: 0.591725844285714

 $00:50:45.421 \rightarrow 00:50:47.990$ who may may represent the best target

NOTE Confidence: 0.591725844285714

 $00:50:47.990 \rightarrow 00:50:50.740$ for treatment as well sake at the end.

NOTE Confidence: 0.591725844285714

 $00:50:50.740 \longrightarrow 00:50:54.100$ So what does lecanu mob do for amyloid?

NOTE Confidence: 0.591725844285714

 $00:50:54.100 \longrightarrow 00:50:55.156$ First of all?

NOTE Confidence: 0.591725844285714

 $00{:}50{:}55{.}156 \dashrightarrow 00{:}50{:}58{.}720$ Well, we saw what it did for amyloid pet.

NOTE Confidence: 0.591725844285714

 $00:50:58.720 \longrightarrow 00:51:00.540$ What about soluble amyloid,

NOTE Confidence: 0.591725844285714

 $00:51:00.540 \longrightarrow 00:51:03.884$ such as a curse in super spinal

NOTE Confidence: 0.591725844285714

00:51:03.884 --> 00:51:05.459 fluid and plasma?

NOTE Confidence: 0.591725844285714

 $00:51:05.460 \longrightarrow 00:51:08.500$ And that's what's shown here.

NOTE Confidence: 0.591725844285714

 $00:51:08.500 \rightarrow 00:51:09.814$ On the left,

 $00:51:09.814 \rightarrow 00:51:12.880$ we're looking at lacanada effects on CSF,

NOTE Confidence: 0.591725844285714

 $00:51:12.880 \longrightarrow 00:51:15.008$ Abeta 40 and 42.

NOTE Confidence: 0.591725844285714

00:51:15.008 --> 00:51:17.190 Remember, 42 is the more important one,

NOTE Confidence: 0.591725844285714

 $00:51:17.190 \longrightarrow 00:51:18.183$ the malignant one.

NOTE Confidence: 0.591725844285714

 $00:51:18.183 \longrightarrow 00:51:19.507$ In the upper right,

NOTE Confidence: 0.591725844285714

 $00:51:19.510 \longrightarrow 00:51:22.561$ we're looking at the ratio of 42 to 40

NOTE Confidence: 0.591725844285714

 $00:51:22.561 \longrightarrow 00:51:26.329$ and in the lower right we're looking at

NOTE Confidence: 0.591725844285714

 $00:51:26.329 \rightarrow 00:51:29.138$ the corresponding ratio in blood plasma.

NOTE Confidence: 0.591725844285714

 $00:51:29.140 \longrightarrow 00:51:31.006$ Overall, one thing to note is

NOTE Confidence: 0.591725844285714

00:51:31.006 --> 00:51:32.790 that in in Alzheimer's disease,

NOTE Confidence: 0.591725844285714

 $00:51:32.790 \rightarrow 00:51:35.730$ actually these all go down,

NOTE Confidence: 0.591725844285714

 $00:51:35.730 \longrightarrow 00:51:36.999$ not up because,

NOTE Confidence: 0.591725844285714

 $00:51:36.999 \rightarrow 00:51:39.960$ and that's thought to occur because they're

NOTE Confidence: 0.591725844285714

 $00:51:40.034 \rightarrow 00:51:43.184$ being aggregated and deposited in the brain,

NOTE Confidence: 0.591725844285714

 $00{:}51{:}43.190 \dashrightarrow 00{:}51{:}44.950$ you know, as plaques.

00:51:44.950 --> 00:51:47.262 So up is good, you know,

NOTE Confidence: 0.591725844285714

 $00{:}51{:}47{.}262 \dashrightarrow 00{:}51{:}48{.}090$ in these cases.

NOTE Confidence: 0.591725844285714

 $00{:}51{:}48.090 \dashrightarrow 00{:}51{:}50.322$ And what you can see is that although

NOTE Confidence: 0.591725844285714

 $00:51:50.322 \rightarrow 00:51:52.810$ there's no effective lukianov on EBITDA 40,

NOTE Confidence: 0.591725844285714

 $00{:}51{:}52{.}810 \dashrightarrow 00{:}51{:}56{.}202$ the more important a beta 42, you know,

NOTE Confidence: 0.591725844285714

 $00:51:56.202 \rightarrow 00:51:59.460$ there's a definite normalizing of the A beta.

NOTE Confidence: 0.591725844285714

 $00:51:59.460 \dashrightarrow 00:52:01.264$ Aggregation process and that's

NOTE Confidence: 0.591725844285714

 $00:52:01.264 \longrightarrow 00:52:04.376$ also shown in the ratio of abeta

NOTE Confidence: 0.591725844285714

 $00{:}52{:}04{.}376 \dashrightarrow 00{:}52{:}06{.}644$ 42 to 40 and it's even shown

NOTE Confidence: 0.591725844285714

 $00:52:06.644 \longrightarrow 00:52:09.037$ in the same ratio in plasma.

NOTE Confidence: 0.752258933333333

 $00:52:11.320 \longrightarrow 00:52:13.870$ What about Tau?

NOTE Confidence: 0.752258933333333

 $00{:}52{:}13.870 \dashrightarrow 00{:}52{:}17.958$ Well, with Tau there are two main.

NOTE Confidence: 0.752258933333333

00:52:17.960 - 00:52:19.630 Things that are being measured,

NOTE Confidence: 0.752258933333333

 $00{:}52{:}19.630 \dashrightarrow 00{:}52{:}21.478$ there's the phosphorylation of

NOTE Confidence: 0.752258933333333

 $00:52:21.478 \dashrightarrow 00:52:24.739$ soluble Tau which is thought to be

NOTE Confidence: 0.752258933333333

 $00:52:24.739 \rightarrow 00:52:27.229$ an early marker of Tau pathogenesis,

 $00:52:27.230 \longrightarrow 00:52:29.410$ and that's what's shown here.

NOTE Confidence: 0.752258933333333

 $00{:}52{:}29{.}410 \dashrightarrow 00{:}52{:}32{.}380$ What we can see is that for phospho

NOTE Confidence: 0.752258933333333

 $00:52:32.380 \rightarrow 00:52:35.800$ Tau 181 steady increases in people

NOTE Confidence: 0.752258933333333

 $00{:}52{:}35{.}800 \dashrightarrow 00{:}52{:}38{.}794$ on place bo and decreases relative

NOTE Confidence: 0.752258933333333

 $00:52:38.794 \rightarrow 00:52:42.334$ to that and people taking liking

NOTE Confidence: 0.752258933333333

 $00{:}52{:}42{.}334 \dashrightarrow 00{:}52{:}45{.}619$ amab in both CSF and plasma.

NOTE Confidence: 0.81702165

 $00:52:48.480 \rightarrow 00:52:52.647$ Tao pet on the other hand is measuring the.

NOTE Confidence: 0.81702165

 $00:52:52.650 \rightarrow 00:52:55.200$ The is looking at the aggregation

NOTE Confidence: 0.81702165

 $00:52:55.200 \longrightarrow 00:52:59.750$ you know of Tau into.

NOTE Confidence: 0.81702165

00:52:59.750 --> 00:53:02.066 Uh deposited as neurofibrillary

NOTE Confidence: 0.81702165

 $00{:}53{:}02.066 \dashrightarrow 00{:}53{:}04.961$ tangles or dystrophic neurites in

NOTE Confidence: 0.81702165

 $00{:}53{:}04{.}961 \dashrightarrow 00{:}53{:}08{.}066$ brain can be measured on a PET scan.

NOTE Confidence: 0.81702165

 $00{:}53{:}08{.}070 \dashrightarrow 00{:}53{:}10{.}653$ In this case we're looking at pet

NOTE Confidence: 0.81702165

 $00:53:10.653 \rightarrow 00:53:12.829$ data from multiple brain regions.

NOTE Confidence: 0.81702165

 $00{:}53{:}12.830 \dashrightarrow 00{:}53{:}14.720$ Although I should point out that the

 $00:53:14.720 \rightarrow 00:53:16.579$ ones of pre specified interest were

NOTE Confidence: 0.81702165

00:53:16.579 --> 00:53:18.896 in the temporal lobe you know which

NOTE Confidence: 0.81702165

 $00{:}53{:}18{.}961 \dashrightarrow 00{:}53{:}20{.}926$ are represent earlier Brock stages.

NOTE Confidence: 0.81702165

 $00:53:20.930 \dashrightarrow 00:53:25.763$ And what we can see here is that for NOTE Confidence: 0.81702165

 $00{:}53{:}25{.}770 \dashrightarrow 00{:}53{:}27{.}850$ three different temporal lobe regions

NOTE Confidence: 0.81702165

 $00{:}53{:}27.850 \dashrightarrow 00{:}53{:}29.930$ and medial temporal lobe so-called.

NOTE Confidence: 0.81702165

 $00{:}53{:}29{.}930 \dashrightarrow 00{:}53{:}32{.}678$ Meta temporal and a whole temporal.

NOTE Confidence: 0.81702165

 $00:53:32.680 \longrightarrow 00:53:34.438$ In all cases,

NOTE Confidence: 0.81702165

00:53:34.438 --> 00:53:37.368 there was a statistically significant

NOTE Confidence: 0.81702165

 $00{:}53{:}37{.}368 \dashrightarrow 00{:}53{:}39{.}400$ blunting bilican amab compared

NOTE Confidence: 0.81702165

 $00:53:39.400 \longrightarrow 00:53:41.080$ to the placebo group.

NOTE Confidence: 0.81702165

00:53:41.080 --> 00:53:42.480 You know, with increasing,

NOTE Confidence: 0.81702165

00:53:42.480 --> 00:53:43.180 you know,

NOTE Confidence: 0.81702165

 $00:53:43.180 \longrightarrow 00:53:45.210$ Tau deposition on PET scan.

NOTE Confidence: 0.7373050826666667

 $00{:}53{:}49{.}000 \dashrightarrow 00{:}53{:}51{.}946$ One measure of end of neurodegeneration

NOTE Confidence: 0.737305082666667

 $00{:}53{:}51{.}946 \dashrightarrow 00{:}53{:}54{.}424$ would be volumetric MRI and

- NOTE Confidence: 0.737305082666667
- $00:53:54.424 \longrightarrow 00:53:56.168$ that's shown here.
- NOTE Confidence: 0.737305082666667
- $00:53:56.170 \longrightarrow 00:53:58.025$ First of all in the top row
- NOTE Confidence: 0.737305082666667
- $00{:}53{:}58.025 \dashrightarrow 00{:}53{:}59.848$ we're looking at the effects of
- NOTE Confidence: 0.737305082666667
- $00:53:59.848 \longrightarrow 00:54:01.774$ lecan amab on whole brain volume,
- NOTE Confidence: 0.7373050826666667
- $00{:}54{:}01{.}780 \dashrightarrow 00{:}54{:}03{.}448$ cortical thickness and
- NOTE Confidence: 0.737305082666667
- 00:54:03.448 --> 00:54:05.116 lateral ventricular volume.
- NOTE Confidence: 0.7373050826666667
- $00:54:05.120 \dashrightarrow 00:54:07.740$ And maybe paradoxically Kanab is
- NOTE Confidence: 0.737305082666667
- $00:54:07.740 \longrightarrow 00:54:09.836$ associated with greater atrophy
- NOTE Confidence: 0.7373050826666667
- $00:54:09.836 \longrightarrow 00:54:12.139$ and all of these measures.
- NOTE Confidence: 0.737305082666667
- $00:54:12.140 \longrightarrow 00:54:13.645$ Now this is something that's
- NOTE Confidence: 0.737305082666667
- 00:54:13.645 00:54:15.548 been seen many times before now
- NOTE Confidence: 0.737305082666667
- $00{:}54{:}15{.}548 \dashrightarrow 00{:}54{:}17{.}243$ with anti amyloid the rapies and
- NOTE Confidence: 0.737305082666667
- $00{:}54{:}17{.}243 \dashrightarrow 00{:}54{:}18{.}599$ and one simple explanation.
- NOTE Confidence: 0.737305082666667
- $00:54:18.600 \rightarrow 00:54:21.864$ Maybe simply that it represents plaque
- NOTE Confidence: 0.737305082666667
- $00{:}54{:}21{.}864 \dashrightarrow 00{:}54{:}24{.}690$ clearance which which reduces volume.
- NOTE Confidence: 0.737305082666667

 $00{:}54{:}24.690 \dashrightarrow 00{:}54{:}26.860$ The bottom row shows hippocampal

NOTE Confidence: 0.737305082666667

 $00{:}54{:}26{.}860 \dashrightarrow 00{:}54{:}29{.}872$ volumes and in this case that effect

NOTE Confidence: 0.737305082666667

 $00{:}54{:}29.872 \dashrightarrow 00{:}54{:}33.240$ is not seen and in fact like Kanab

NOTE Confidence: 0.737305082666667

 $00:54:33.336 \rightarrow 00:54:36.684$ is associated with less atrophy in

NOTE Confidence: 0.737305082666667

 $00:54:36.684 \rightarrow 00:54:39.840$ hippocampal volumes at end of study.

NOTE Confidence: 0.737305082666667

 $00:54:39.840 \rightarrow 00:54:43.648$ So where do we go next from here?

NOTE Confidence: 0.7373050826666667

 $00{:}54{:}43{.}650 \dashrightarrow 00{:}54{:}46{.}251$ You know we can't a mab may be ready for

NOTE Confidence: 0.737305082666667

 $00:54:46.251 \rightarrow 00:54:48.256$ the clinic you know remains remains

NOTE Confidence: 0.737305082666667

 $00:54:48.256 \dashrightarrow 00:54:51.387$ to be seen by you know FDA and and CMS.

NOTE Confidence: 0.737305082666667

 $00:54:51.390 \longrightarrow 00:54:54.462$ It did receive the accelerated approval

NOTE Confidence: 0.737305082666667

 $00{:}54{:}54{.}462 \dashrightarrow 00{:}54{:}57{.}540$ based on plaque clearance January 6th.

NOTE Confidence: 0.7373050826666667

 $00{:}54{:}57{.}540 \dashrightarrow 00{:}54{:}58{.}970$ Umm, and it was submitted.

NOTE Confidence: 0.7373050826666667

 $00{:}54{:}58{.}970 \dashrightarrow 00{:}55{:}01{.}538$ They submitted for traditional approval on

NOTE Confidence: 0.737305082666667

 $00:55:01.538 \rightarrow 00:55:05.080$ January 6th with a decision likely to occur,

NOTE Confidence: 0.737305082666667

00:55:05.080 --> 00:55:05.712 you know,

NOTE Confidence: 0.737305082666667

 $00:55:05.712 \longrightarrow 00:55:06.660$ probably late spring.

 $00:55:06.660 \rightarrow 00:55:07.680$ And then the question will be,

NOTE Confidence: 0.737305082666667

00:55:07.680 --> 00:55:10.760 will CMS revisit coverage decision?

NOTE Confidence: 0.737305082666667

 $00:55:10.760 \rightarrow 00:55:13.304$ I just want to highlight here in the

NOTE Confidence: 0.737305082666667

 $00:55:13.304 \rightarrow 00:55:15.637$ middle though that this whole issue

NOTE Confidence: 0.7373050826666667

 $00{:}55{:}15.637 \dashrightarrow 00{:}55{:}17.672$ of accelerated approval based on

NOTE Confidence: 0.737305082666667

 $00:55:17.672 \rightarrow 00:55:19.678$ biomarker is really controversial.

NOTE Confidence: 0.7373050826666667

00:55:19.680 --> 00:55:21.240 And for anyone interested,

NOTE Confidence: 0.737305082666667

 $00:55:21.240 \longrightarrow 00:55:23.580$ we're going to have a webinar

NOTE Confidence: 0.7373050826666667

00:55:23.655 --> 00:55:25.119 debate next Thursday.

NOTE Confidence: 0.737305082666667

 $00:55:25.120 \longrightarrow 00:55:26.480$ Dennis Selkoe's going to

NOTE Confidence: 0.7373050826666667

 $00:55:26.480 \longrightarrow 00:55:27.500$ take the affirmative.

NOTE Confidence: 0.737305082666667

 $00:55:27.500 \longrightarrow 00:55:28.970$ That this is a ready,

NOTE Confidence: 0.737305082666667

 $00:55:28.970 \longrightarrow 00:55:29.994$ we're ready for this,

NOTE Confidence: 0.737305082666667

 $00{:}55{:}29{.}994 \dashrightarrow 00{:}55{:}32{.}090$ so I'm going to take the negative.

NOTE Confidence: 0.7373050826666667

 $00:55:32.090 \longrightarrow 00:55:32.876$ Here's the link.

 $00:55:32.876 \longrightarrow 00:55:35.087$ We can put it in the chat and

NOTE Confidence: 0.737305082666667

00:55:35.087 --> 00:55:36.923 if anyone has any trouble you

NOTE Confidence: 0.737305082666667

 $00:55:36.923 \rightarrow 00:55:39.187$ can just e-mail me and I'll make

NOTE Confidence: 0.737305082666667

 $00:55:39.187 \rightarrow 00:55:40.782$ sure that you get registered.

NOTE Confidence: 0.737305082666667

 $00{:}55{:}40{.}790 \dashrightarrow 00{:}55{:}43{.}135$ The other where to next is is

NOTE Confidence: 0.737305082666667

 $00:55:43.135 \longrightarrow 00:55:45.450$ where we go scientifically.

NOTE Confidence: 0.737305082666667

 $00:55:45.450 \rightarrow 00:55:48.106$ And I think these results really beg the

NOTE Confidence: 0.737305082666667

 $00:55:48.106 \rightarrow 00:55:50.109$ question about earlier intervention,

NOTE Confidence: 0.7373050826666667

 $00{:}55{:}50{.}110 \dashrightarrow 00{:}55{:}52{.}384$ you know then clarity AD which

NOTE Confidence: 0.737305082666667

 $00:55:52.384 \rightarrow 00:55:54.530$ was in early symptomatic disease,

NOTE Confidence: 0.737305082666667

 $00:55:54.530 \longrightarrow 00:55:56.986$ I think we need to go to pre

NOTE Confidence: 0.7373050826666667

 $00:55:56.986 \rightarrow 00:55:58.595$ symptomatic disease which is what

NOTE Confidence: 0.7373050826666667

00:55:58.595 --> 00:56:00.702 the ahead study does and this

NOTE Confidence: 0.737305082666667

 $00:56:00.702 \dashrightarrow 00:56:02.857$ study was started already about

NOTE Confidence: 0.7373050826666667

 $00{:}56{:}02.857 \dashrightarrow 00{:}56{:}04.520$ almost three years ago.

NOTE Confidence: 0.737305082666667

 $00:56:04.520 \longrightarrow 00:56:06.920$ And we fortunately chose the cannabis

- NOTE Confidence: 0.737305082666667
- $00:56:06.920 \rightarrow 00:56:09.959$ the drug before we knew these results.
- NOTE Confidence: 0.737305082666667
- $00:56:09.960 \longrightarrow 00:56:12.606$ But there are two parts of.
- NOTE Confidence: 0.737305082666667
- $00:56:12.610 \longrightarrow 00:56:14.830$ The head study people in the
- NOTE Confidence: 0.737305082666667
- $00:56:14.830 \longrightarrow 00:56:17.475$ so-called a 4-5 arm have elevated
- NOTE Confidence: 0.7373050826666667
- $00:56:17.475 \longrightarrow 00:56:20.175$ and clearly elevated brain amyloid.
- NOTE Confidence: 0.737305082666667
- $00:56:20.180 \longrightarrow 00:56:23.270$ In the A3 portion they have
- NOTE Confidence: 0.7373050826666667
- $00:56:23.270 \longrightarrow 00:56:24.815$ sub threshold elevation,
- NOTE Confidence: 0.737305082666667
- $00:56:24.820 \rightarrow 00:56:26.794$ you don't it's it looks visually normal
- NOTE Confidence: 0.7373050826666667
- $00{:}56{:}26{.}794 \dashrightarrow 00{:}56{:}29{.}144$ but we know these folks are destined
- NOTE Confidence: 0.737305082666667
- $00:56:29.144 \rightarrow 00:56:30.954$ for further you know accumulation.
- NOTE Confidence: 0.737305082666667
- 00:56:30.960 -> 00:56:33.876 So maybe even a better point
- NOTE Confidence: 0.737305082666667
- $00{:}56{:}33{.}876 \dashrightarrow 00{:}56{:}35{.}334$ of of intervention.
- NOTE Confidence: 0.737305082666667
- $00{:}56{:}35{.}340 \dashrightarrow 00{:}56{:}38{.}088$ Your head study design is shown
- NOTE Confidence: 0.737305082666667
- $00{:}56{:}38{.}088 \dashrightarrow 00{:}56{:}41{.}578$ here to four year long trial 5050
- NOTE Confidence: 0.737305082666667
- 00:56:41.578 --> 00:56:44.543 randomization people in the A45
- NOTE Confidence: 0.737305082666667

 $00:56:44.543 \rightarrow 00:56:46.808$ arm with clearly elevated amyloid.

NOTE Confidence: 0.737305082666667

 $00:56:46.810 \longrightarrow 00:56:49.127$ Start out every two week infusions for

NOTE Confidence: 0.737305082666667

 $00:56:49.127 \rightarrow 00:56:51.968$ two years and then go to every four weeks.

NOTE Confidence: 0.737305082666667

 $00{:}56{:}51{.}970 \dashrightarrow 00{:}56{:}53{.}282$ Those with the intermediate

NOTE Confidence: 0.737305082666667

 $00:56:53.282 \longrightarrow 00:56:55.666$ levels can just be on every four

NOTE Confidence: 0.737305082666667

 $00{:}56{:}55{.}666$ --> $00{:}56{:}57{.}406$ weeks for the entire duration.

NOTE Confidence: 0.7373050826666667

 $00:56:57.410 \longrightarrow 00:57:00.450$ Maybe a three study.

NOTE Confidence: 0.737305082666667

 $00:57:00.450 \rightarrow 00:57:04.050$ So in summary of what I've shown you,

NOTE Confidence: 0.737305082666667

 $00{:}57{:}04.050 \dashrightarrow 00{:}57{:}06.708$ the cannab treatment met all primary

NOTE Confidence: 0.737305082666667

 $00:57:06.708 \rightarrow 00:57:08.480$ and secondary endpoints versus

NOTE Confidence: 0.737305082666667

 $00{:}57{:}08{.}548{\:}{-}{-}{>}00{:}57{:}11{.}242$ place bo at 18 months with highly

NOTE Confidence: 0.7373050826666667

 $00:57:11.242 \rightarrow 00:57:13.038$ significant differences starting at

NOTE Confidence: 0.833930258636364

 $00{:}57{:}13.112 \dashrightarrow 00{:}57{:}15.270$ six months. And I think one of

NOTE Confidence: 0.833930258636364

 $00:57:15.270 \rightarrow 00:57:17.087$ the most compelling things is how

NOTE Confidence: 0.833930258636364

00:57:17.087 --> 00:57:19.019 consistent the results are across a

NOTE Confidence: 0.833930258636364

 $00:57:19.019 \rightarrow 00:57:21.479$ broad range of endpoints and subgroups.

 $00{:}57{:}21{.}480 \dashrightarrow 00{:}57{:}24{.}581$ The safety profile of LA Canada I

NOTE Confidence: 0.833930258636364

00:57:24.581 --> 00:57:26.637 would consider acceptable with lower

NOTE Confidence: 0.833930258636364

00:57:26.637 --> 00:57:29.395 rates of Aria E compared to other

NOTE Confidence: 0.833930258636364

 $00:57:29.395 \rightarrow 00:57:31.820$ published studies with other antibodies.

NOTE Confidence: 0.833930258636364

 $00:57:31.820 \longrightarrow 00:57:34.268$ Biomarker studies revealed that we cannot

NOTE Confidence: 0.833930258636364

 $00{:}57{:}34{.}268 \dashrightarrow 00{:}57{:}37{.}024$ have improved both of the essential

NOTE Confidence: 0.833930258636364

 $00:57:37.024 \rightarrow 00:57:39.140$ biological features of Alzheimer's,

NOTE Confidence: 0.833930258636364

00:57:39.140 --> 00:57:42.380 both amyloid and Tau and they did it by Pat,

NOTE Confidence: 0.833930258636364

 $00{:}57{:}42{.}380 \dashrightarrow 00{:}57{:}45{.}248$ CSF and blood plasma.

NOTE Confidence: 0.833930258636364

 $00{:}57{:}45{.}248 \dashrightarrow 00{:}57{:}48{.}116$ And this indicates biological

NOTE Confidence: 0.833930258636364

 $00{:}57{:}48.116 \dashrightarrow 00{:}57{:}49.550$ disease modification.

NOTE Confidence: 0.833930258636364

 $00{:}57{:}49{.}550 \dashrightarrow 00{:}57{:}51{.}370$ The brain MRI volumetric analysis

NOTE Confidence: 0.833930258636364

 $00{:}57{:}51{.}370 \dashrightarrow 00{:}57{:}53{.}747$ indicated that like Canada was associated

NOTE Confidence: 0.833930258636364

 $00{:}57{:}53.747 \dashrightarrow 00{:}57{:}55.747$ with reduced hippocampal atrophy,

NOTE Confidence: 0.833930258636364

 $00{:}57{:}55{.}750 \dashrightarrow 00{:}57{:}59{.}122$ but greater global and cortical atrophy

 $00:57:59.122 \rightarrow 00:58:02.523$ possibly related to amyloid removal like

NOTE Confidence: 0.833930258636364

00:58:02.523 --> 00:58:04.888 Kanab has received accelerated approval

NOTE Confidence: 0.833930258636364

 $00{:}58{:}04{.}888 \dashrightarrow 00{:}58{:}07{.}817$ with the decision on full approval

NOTE Confidence: 0.833930258636364

 $00:58:07.817 \rightarrow 00:58:10.709$ pending and it's uncertain whether CMS,

NOTE Confidence: 0.833930258636364

00:58:10.710 --> 00:58:11.818 you know,

NOTE Confidence: 0.833930258636364

 $00{:}58{:}11.818 \dashrightarrow 00{:}58{:}14.034$ Medicare will revise coverage

NOTE Confidence: 0.833930258636364

 $00:58:14.034 \longrightarrow 00:58:15.823$ decision and last you.

NOTE Confidence: 0.833930258636364

 $00:58:15.823 \rightarrow 00:58:18.700$ Had to study is investigating were earlier.

NOTE Confidence: 0.833930258636364

 $00:58:18.700 \longrightarrow 00:58:21.020$ Whether early or pre,

NOTE Confidence: 0.833930258636364

 $00:58:21.020 \rightarrow 00:58:23.340$ symptomatic intervention may be

NOTE Confidence: 0.833930258636364

 $00:58:23.340 \rightarrow 00:58:26.349$ associated with greater effect sizes.

NOTE Confidence: 0.833930258636364

 $00{:}58{:}26{.}350 \dashrightarrow 00{:}58{:}29{.}078$ So I I thank you for your attention

NOTE Confidence: 0.833930258636364

 $00:58:29.078 \longrightarrow 00:58:30.999$ and I'll take questions.