WEBVTT

NOTE duration:"00:58:31"

NOTE recognizability:0.806

NOTE language:en-us

NOTE Confidence: 0.85747489

00:00:00.000 --> 00:00:04.340 Very kind introduction. By the way,

NOTE Confidence: 0.85747489

00:00:04.340 --> 00:00:06.510 you didn't hold me back in residency,

NOTE Confidence: 0.85747489

00:00:06.510 --> 00:00:08.940 except for maybe the the raucous

NOTE Confidence: 0.85747489

00:00:08.940 --> 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 --> 00:00:26.620 So just get this reset.

NOTE Confidence: 0.861854593333333

00:00:43.130 --> 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 --> 00:00:58.084 degrees of familiarity with with

NOTE Confidence: 0.861854593333333

00:00:58.084 --> 00:01:01.700 what I'm going to talk about.

NOTE Confidence: 0.861854593333333

00:01:01.700 --> 00:01:04.514 You know in particular the the recent

NOTE Confidence: 0.861854593333333

00:01:04.514 --> 00:01:06.878 controversy in the news about the

NOTE Confidence: 0.861854593333333

00:01:06.878 --> 00:01:09.121 first so-called disease modifying

NOTE Confidence: 0.861854593333333

00:01:09.121 --> 00:01:11.629 therapies 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 --> 00:01:15.524 they came to the news I'd you can't

NOTE Confidence: 0.861854593333333

00:01:15.530 --> 00:01:18.160 approved the first disease modifying

NOTE Confidence: 0.861854593333333

00:01:18.160 --> 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 --> 00:01:23.670 it wasn't full approval.

NOTE Confidence: 0.861854593333333

00:01:23.670 --> 00:01:26.980 It was accelerated approval based on a

NOTE Confidence: 0.861854593333333

00:01:26.980 --> 00:01:29.470 biomarker and that's plaque clearance.

NOTE Confidence: 0.861854593333333

00:01:29.470 --> 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 --> 00:01:37.280 Culminating about 10 months later in the

NOTE Confidence: 0.861854593333333

00:01:37.280 --> 00:01:40.650 decision by CMS not to pay for the drug.

NOTE Confidence: 0.861854593333333

00:01:40.650 --> 00:01:43.770 And then as the dust settled for that,

NOTE Confidence: 0.861854593333333

00:01:43.770 --> 00:01:46.356 we started to hear about lacanada

NOTE Confidence: 0.861854593333333

00:01:46.356 --> 00:01:48.483 different drug that actually appeared

NOTE Confidence: 0.861854593333333

00:01:48.483 --> 00:01:51.147 to meet the bar for full approval in

NOTE Confidence: 0.861854593333333

00:01:51.147 --> 00:01:53.987 in a in a more straightforward manner,

NOTE Confidence: 0.861854593333333

00:01:53.990 --> 00:01:55.922 although as we're going to see the

NOTE Confidence: 0.861854593333333

00:01:55.922 --> 00:01:57.562 Kanab has its own uncertainties

NOTE Confidence: 0.861854593333333

00:01:57.562 --> 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 --> 00:02:04.130 to be talking about today.

NOTE Confidence: 0.861854593333333

00:02:04.130 --> 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 --> 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 --> 00:02:14.569 for the conductive conduct of

NOTE Confidence: 0.861854593333333

00:02:14.569 --> 00:02:16.065 trials with these drugs.

NOTE Confidence: 0.861854593333333

00:02:16.070 --> 00:02:18.182 And I'm also a paid consultant

NOTE Confidence: 0.861854593333333

00:02:18.182 --> 00:02:20.418 to Asahi who makes like canaman.

NOTE Confidence: 0.861854593333333

00:02:20.418 --> 00:02:23.123 I don't have any any financial stake

NOTE Confidence: 0.861854593333333

00:02:23.123 --> 00:02:25.827 in the in the success of these drugs.

NOTE Confidence: 0.861854593333333

00:02:25.830 --> 00:02:28.098 And almost all of what I'm going to show

NOTE Confidence: 0.861854593333333

00:02:28.098 --> 00:02:30.366 you is from peer reviewed publication,

NOTE Confidence: 0.861854593333333

00:02:30.370 --> 00:02:32.182 mainly that the New England Journal

NOTE Confidence: 0.861854593333333

00:02:32.182 --> 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 --> 00:02:39.097 when I'm showing you something

NOTE Confidence: 0.861854593333333

00:02:39.097 --> 00:02:41.257 that is not peer reviewed.

NOTE Confidence: 0.861854593333333

00:02:41.260 --> 00:02:44.316 Well, so in in talking about like Canada,

NOTE Confidence: 0.861854593333333

00:02:44.320 --> 00:02:48.278 I think we need to go back to the the whole

NOTE Confidence: 0.861854593333333

00:02:48.278 --> 00:02:52.094 controversy with the earlier drug aducanumab.

NOTE Confidence: 0.861854593333333

00:02:52.100 --> 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 --> 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 --> 00:03:01.952 in something I'm almost concerned that

NOTE Confidence: 0.861854593333333

00:03:01.952 --> 00:03:05.358 they waited a day so they didn't try

NOTE Confidence: 0.861854593333333

00:03:05.358 --> 00:03:07.740 to eclipse the anniversary of D-Day,

NOTE Confidence: 0.861854593333333

00:03:07.740 --> 00:03:10.736 but it was, it was huge news,

NOTE Confidence: 0.861854593333333

00:03:10.740 --> 00:03:12.375 but then almost.

NOTE Confidence: 0.861854593333333

00:03:12.375 --> 00:03:14.555 Instantaneously came the backlash,

NOTE Confidence: 0.861854593333333

00:03:14.560 --> 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 --> 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 --> 00:03:27.358 what the controversy was about.

NOTE Confidence: 0.861854593333333

00:03:27.360 --> 00:03:30.522 But I think to do that I need to do a

NOTE Confidence: 0.861854593333333

00:03:30.522 --> 00:03:32.960 little background on the pathogenesis

NOTE Confidence: 0.861854593333333

00:03:32.960 --> 00:03:36.500 and mechanisms that underlie these drugs,

NOTE Confidence: 0.861854593333333

00:03:36.500 --> 00:03:39.224 and then more detail about the

NOTE Confidence: 0.861854593333333

00:03:39.224 --> 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 --> 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 --> 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 --> 00:03:54.750 mechanism of amyloid production.

NOTE Confidence: 0.861854593333333

00:03:54.750 --> 00:03:58.126 So what we're looking at here is the

NOTE Confidence: 0.861854593333333

00:03:58.126 --> 00:04:01.089 production of the toxic abeta peptide.

NOTE Confidence: 0.861854593333333

00:04:01.090 --> 00:04:03.813 I think you can see my cursor

NOTE Confidence: 0.861854593333333

00:04:03.813 --> 00:04:06.190 from the the amyloid precursor

NOTE Confidence: 0.861854593333333

00:04:06.190 --> 00:04:09.526 protein over here on the left.

NOTE Confidence: 0.861854593333333

00:04:09.530 --> 00:04:14.786 So this AP spans the the cell membrane then.

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NOTE Confidence: 0.861854593333333

00:04:14.790 --> 00:04:17.568 The neuronal membrane in this case.

NOTE Confidence: 0.861854593333333

00:04:17.570 --> 00:04:20.132 And it is cleaved by the

NOTE Confidence: 0.861854593333333

00:04:20.132 --> 00:04:21.840 enzymes beta and gamma

NOTE Confidence: 0.786859445

00:04:21.932 --> 00:04:25.924 secretase to form the toxic a beta fragment.

NOTE Confidence: 0.786859445

00:04:25.930 --> 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 --> 00:04:34.390 where it's clear by gamma secretase.

NOTE Confidence: 0.786859445

00:04:34.390 --> 00:04:36.580 And the main major forms as

NOTE Confidence: 0.786859445

00:04:36.580 --> 00:04:38.946 we'll see are in a beta 42,

NOTE Confidence: 0.786859445

00:04:38.946 --> 00:04:40.210 a little longer form.

NOTE Confidence: 0.786859445

00:04:40.210 --> 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 --> 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 --> 00:04:52.194 and what are those?

NOTE Confidence: 0.786859445

00:04:52.200 --> 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 --> 00:05:02.672 species oligomers and and larger

NOTE Confidence: 0.786859445

00:05:02.672 --> 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 --> 00:05:13.109 also aggregate further into plaques.

NOTE Confidence: 0.786859445

00:05:13.110 --> 00:05:14.174 And overall,

NOTE Confidence: 0.786859445

00:05:14.174 --> 00:05:17.366 the goal of these therapies though

NOTE Confidence: 0.786859445

00:05:17.366 --> 00:05:21.270 is to alter the balance between

NOTE Confidence: 0.786859445

00:05:21.270 --> 00:05:24.685 production and clearance so the

NOTE Confidence: 0.786859445

00:05:24.685 --> 00:05:27.837 antibodies aim to clear amyloid

NOTE Confidence: 0.786859445

00:05:27.837 --> 00:05:30.792 and alter the balance favorably.

NOTE Confidence: 0.786859445

00:05:30.800 --> 00:05:34.058 And what what are these antibodies?

NOTE Confidence: 0.786859445

00:05:34.060 --> 00:05:37.795 Such as Lacan Amab and 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 --> 00:05:40.808 that's that's shown here in in a

NOTE Confidence: 0.786859445

00:05:40.808 --> 00:05:43.639 somewhat busy table that I that I do

NOTE Confidence: 0.786859445

00:05:43.639 --> 00:05:45.990 really want to simplify a great deal.

NOTE Confidence: 0.786859445

00:05:45.990 --> 00:05:50.966 So these are in the case of aducanumab,

NOTE Confidence: 0.786859445

00:05:50.970 --> 00:05:54.134 this is a an actual human antibody

NOTE Confidence: 0.786859445

00:05:54.134 --> 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 --> 00:06:02.510 Been cloned and mass produced.

NOTE Confidence: 0.786859445

00:06:02.510 --> 00:06:05.270 And now it's administered every four

NOTE Confidence: 0.786859445

00:06:05.270 --> 00:06:07.950 weeks intravenously as a treatment.

NOTE Confidence: 0.786859445

00:06:07.950 --> 00:06:10.866 Of note is that it's what we call an

NOTE Confidence: 0.786859445

00:06:10.870 --> 00:06:15.886 n-terminal antibody and the a beta

NOTE Confidence: 0.786859445

00:06:15.890 --> 00:06:18.585 42 is shown down here in purple.

NOTE Confidence: 0.786859445

00:06:18.590 --> 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 --> 00:06:27.648 And so how'd you can't remember

NOTE Confidence: 0.786859445

00:06:27.648 --> 00:06:29.612 by buying certain amino acids

NOTE Confidence: 0.786859445

00:06:29.612 --> 00:06:32.340 3 through 6 on the left side?

NOTE Confidence: 0.786859445

00:06:32.340 --> 00:06:35.112 What's important about that is that even

NOTE Confidence: 0.786859445

00:06:35.112 --> 00:06:38.080 when amyloid is aggregated as oligomers,

NOTE Confidence: 0.786859445

00:06:38.080 --> 00:06:39.088 proto fibrils,

NOTE Confidence: 0.786859445

00:06:39.088 --> 00:06:39.592 plaques.

NOTE Confidence: 0.786859445

00:06:39.592 --> 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 --> 00:06:47.034 so they will still they will

NOTE Confidence: 0.786859445

00:06:47.034 --> 00:06:48.709 still target it and clear it.

NOTE Confidence: 0.865366352857143

00:06:50.870 --> 00:06:53.187 And over on the in the right

NOTE Confidence: 0.865366352857143

00:06:53.187 --> 00:06:55.467 columns you can see the big red,

NOTE Confidence: 0.865366352857143

00:06:55.470 --> 00:06:58.126 yes for all of them are in fibral.

NOTE Confidence: 0.865366352857143

00:06:58.130 --> 00:06:59.929 So if it's an end terminal antibody,

NOTE Confidence: 0.865366352857143

00:06:59.930 --> 00:07:01.746 that's why it targets

NOTE Confidence: 0.865366352857143

00:07:01.746 --> 00:07:03.108 these aggregated species.

NOTE Confidence: 0.865366352857143

00:07:03.110 --> 00:07:05.330 It actually doesn't target

NOTE Confidence: 0.865366352857143

00:07:05.330 --> 00:07:08.105 target monomers to speak of.

NOTE Confidence: 0.865366352857143

00:07:08.110 --> 00:07:09.988 And we can't. Amap is similar.

NOTE Confidence: 0.865366352857143

00:07:09.990 --> 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 --> 00:07:16.904 derived from a mouse antibody but

NOTE Confidence: 0.865366352857143

00:07:16.904 --> 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 --> 00:07:25.926 and so it also binds oligomers

NOTE Confidence: 0.865366352857143

00:07:25.926 --> 00:07:28.480 and proto fibrils in particular,

NOTE Confidence: 0.865366352857143

00:07:28.480 --> 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 --> 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 --> 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 --> 00:07:52.570 one of the original phase one studies,

NOTE Confidence: 0.73357914

00:07:52.570 --> 00:07:54.254 a Phase 1B study.

NOTE Confidence: 0.73357914

00:07:54.254 --> 00:07:57.478 And what we're looking at actually are

NOTE Confidence: 0.73357914

00:07:57.478 --> 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 --> 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 --> 00:08:16.961 through the brain and and high amyloid

NOTE Confidence: 0.73357914

00:08:16.961 --> 00:08:20.480 binding is shown in red followed by yellow.

NOTE Confidence: 0.73357914

00:08:20.480 --> 00:08:22.685 So for example this person on the

NOTE Confidence: 0.73357914

00:08:22.685 --> 00:08:25.179 top row was in the placebo group.

NOTE Confidence: 0.73357914

00:08:25.180 --> 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,

NOTE Confidence: 0.73357914

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

NOTE Confidence: 0.73357914

00:08:33.870 --> 00:08:36.118 but with progressively higher

NOTE Confidence: 0.73357914

00:08:36.118 --> 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 --> 00:08:47.317 in infusions every four weeks you see

NOTE Confidence: 0.73357914

00:08:47.317 --> 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 --> 00:08:56.334 the 10 milligram per kilogram dose which.

NOTE Confidence: 0.73357914

00:08:56.340 --> 00:08:57.976 Is the clinically relevant

NOTE Confidence: 0.73357914

00:08:57.976 --> 00:09:00.430 dose when all of sudden done,

NOTE Confidence: 0.73357914

00:09:00.430 --> 00:09:02.075 this person scan is actually

NOTE Confidence: 0.73357914

00:09:02.075 --> 00:09:04.469 normal at the end of the study.

NOTE Confidence: 0.73357914

00:09:04.470 --> 00:09:06.166 The bit of yellow you see here is

NOTE Confidence: 0.73357914

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00:09:06.166 --> 00:09:08.269 in the white matter and it's what

NOTE Confidence: 0.73357914

00:09:08.269 --> 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 --> 00:09:12.830 with the scan,

NOTE Confidence: 0.73357914

00:09:12.830 --> 00:09:14.720 they would have not been allowed because

NOTE Confidence: 0.73357914

00:09:14.720 --> 00:09:16.956 they didn't have evidence, you know,

NOTE Confidence: 0.73357914

00:09:16.956 --> 00:09:20.267 of of amyloid on their pet scan.

NOTE Confidence: 0.73357914

00:09:20.270 --> 00:09:22.260 So very dramatic plaque clearance.

NOTE Confidence: 0.73357914

00:09:22.260 --> 00:09:23.580 So this is something that we

NOTE Confidence: 0.73357914

00:09:23.580 --> 00:09:24.830 had never ever seen before,

NOTE Confidence: 0.73357914

00:09:24.830 --> 00:09:25.610 you know,

NOTE Confidence: 0.73357914

00:09:25.610 --> 00:09:26.780 until this study.

NOTE Confidence: 0.781168396666667

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

NOTE Confidence: 0.781168396666667

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

NOTE Confidence: 0.781168396666667

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

NOTE Confidence: 0.781168396666667

00:09:34.710 --> 00:09:36.158 They went right from

NOTE Confidence: 0.781168396666667

00:09:36.158 --> 00:09:37.968 phase one to phase three,

NOTE Confidence: 0.781168396666667

00:09:37.970 --> 00:09:40.906 but maybe a mistake as we'll see later.

NOTE Confidence: 0.781168396666667

00:09:40.910 --> 00:09:43.148 Now these now flash forward are

NOTE Confidence: 0.781168396666667

00:09:43.148 --> 00:09:46.153 data from one of the two pivotal

NOTE Confidence: 0.781168396666667

00:09:46.153 --> 00:09:48.533 phase three trials called emerge.

NOTE Confidence: 0.781168396666667

00:09:48.540 --> 00:09:51.746 Um and. What we're looking at here

NOTE Confidence: 0.781168396666667

00:09:51.746 --> 00:09:54.740 again is amyloid plaque clearance,

NOTE Confidence: 0.781168396666667

00:09:54.740 --> 00:09:57.106 but now we're looking at it quantitatively

NOTE Confidence: 0.781168396666667

00:09:57.106 --> 00:09:59.649 and this is now over a year and a

NOTE Confidence: 0.781168396666667

00:09:59.649 --> 00:10:01.878 half instead of a year 78 week trial.

NOTE Confidence: 0.781168396666667

00:10:01.880 --> 00:10:04.225 You can see that the placebo group

NOTE Confidence: 0.781168396666667

00:10:04.225 --> 00:10:06.352 doesn't have much change in the

NOTE Confidence: 0.781168396666667

00:10:06.352 --> 00:10:08.458 amyloid binding over the 18 months,

NOTE Confidence: 0.781168396666667

00:10:08.460 --> 00:10:11.160 but the relevant high dose group,

NOTE Confidence: 0.781168396666667

00:10:11.160 --> 00:10:14.044 mostly 10 megs per kig in purple

NOTE Confidence: 0.781168396666667

00:10:14.044 --> 00:10:16.160 has dramatic plaque clearance.

NOTE Confidence: 0.781168396666667

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

NOTE Confidence: 0.781168396666667

00:10:18.300 --> 00:10:20.012 the quantitation in detail,

NOTE Confidence: 0.781168396666667

00:10:20.020 --> 00:10:22.176 suffice it to say that most of

NOTE Confidence: 0.781168396666667

00:10:22.176 --> 00:10:24.289 these people had normal appearing.

NOTE Confidence: 0.781168396666667

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

NOTE Confidence: 0.781168396666667

00:10:25.748 --> 00:10:29.150 quantitatively at the end of the study.

NOTE Confidence: 0.781168396666667

00:10:29.150 --> 00:10:30.230 But the question then is,

NOTE Confidence: 0.781168396666667

00:10:30.230 --> 00:10:33.308 is that associated with clinical benefit,

NOTE Confidence: 0.781168396666667

00:10:33.310 --> 00:10:36.438 so at least in the case of the?

NOTE Confidence: 0.807918553333333

00:10:38.580 --> 00:10:41.598 Emerged study, the answer was yes.

NOTE Confidence: 0.807918553333333

00:10:41.600 --> 00:10:44.952 So here we're looking at the the primary

NOTE Confidence: 0.807918553333333

00:10:44.952 --> 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 --> 00:10:53.969 of boxes and for for the many of you

NOTE Confidence: 0.807918553333333

00:10:53.969 --> 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 --> 00:11:01.976 the primary outcome in in these trials.

NOTE Confidence: 0.807918553333333

00:11:01.980 --> 00:11:05.620 It's based on an interview with a partner

NOTE Confidence: 0.807918553333333

00:11:05.620 --> 00:11:09.309 caregiver as well as the patient participant.

NOTE Confidence: 0.807918553333333

00:11:09.310 --> 00:11:11.222 Themselves, and it generates

NOTE Confidence: 0.807918553333333

00:11:11.222 --> 00:11:14.090 scores in each of 6 domains.

NOTE Confidence: 0.807918553333333

00:11:14.090 --> 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 --> 00:11:21.310 They're all scored zero to three.

NOTE Confidence: 0.807918553333333

00:11:21.310 --> 00:11:25.250 So the overall Cdr SB score is 0 to 18,

NOTE Confidence: 0.807918553333333

00:11:25.250 --> 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 --> 00:11:36.633 that tend to be bunched with

NOTE Confidence: 0.76115661

00:11:36.633 --> 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 --> 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 --> 00:11:49.996 to the tune of about 1.75.

NOTE Confidence: 0.76115661

00:11:49.996 --> 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 --> 00:11:58.130 which is the relevant group, worsens as well,

NOTE Confidence: 0.76115661

00:11:58.130 --> 00:12:02.550 but about .39 less than the placebo.

NOTE Confidence: 0.76115661

00:12:02.550 --> 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 --> 00:12:13.348 And Umm and this, this is a positive study.

NOTE Confidence: 0.76115661

00:12:13.350 --> 00:12:14.734 Now the problem is,

NOTE Confidence: 0.76115661

00:12:14.734 --> 00:12:17.750 is that the FDA requires two such studies

NOTE Confidence: 0.76115661

00:12:17.750 --> 00:12:19.430 and Biogen had skipped phase two.

NOTE Confidence: 0.76115661

00:12:19.430 --> 00:12:22.090 They might have gotten an opportunity there,

NOTE Confidence: 0.76115661

00:12:22.090 --> 00:12:24.176 but they were required to have a

NOTE Confidence: 0.76115661

00:12:24.176 --> 00:12:26.031 sister study in phase three and

NOTE Confidence: 0.76115661

00:12:26.031 --> 00:12:28.694 that was that was called engage

NOTE Confidence: 0.76115661

00:12:28.694 --> 00:12:32.650 and here are the data for engage.

NOTE Confidence: 0.76115661

00:12:32.650 --> 00:12:35.744 These are the data with the Cdr.

NOTE Confidence: 0.76115661

00:12:35.750 --> 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 --> 00:12:44.758 when it came to the clinical measure,

NOTE Confidence: 0.76115661

00:12:44.760 --> 00:12:48.120 the primary outcome, it was a total bust.

NOTE Confidence: 0.76115661

00:12:48.120 --> 00:12:51.110 You know, there's nothing here.

NOTE Confidence: 0.76115661

00:12:51.110 --> 00:12:52.952 The the worst line in purple

NOTE Confidence: 0.76115661

00:12:52.952 --> 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 --> 00:12:58.048 although it's trivially different

NOTE Confidence: 0.76115661

00:12:58.048 --> 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 --> 00:13:04.910 one very negative study.

NOTE Confidence: 0.76115661

00:13:04.910 --> 00:13:06.800 Now, what to make of that,

NOTE Confidence: 0.76115661

00:13:06.800 --> 00:13:07.382 you know,

NOTE Confidence: 0.76115661

00:13:07.382 --> 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 --> 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 --> 00:13:23.346 that these studies emerge in again and

NOTE Confidence: 0.8920642

00:13:23.346 --> 00:13:26.389 engage really went through quite an ordeal.

NOTE Confidence: 0.8920642

00:13:26.390 --> 00:13:28.886 One that many of you know is that

NOTE Confidence: 0.8920642

00:13:28.886 --> 00:13:31.011 they were actually halted prematurely

NOTE Confidence: 0.8920642

00:13:31.011 --> 00:13:33.849 for a futility analysis which is

NOTE Confidence: 0.8920642

00:13:33.849 --> 00:13:36.837 done commonly in our field where an

NOTE Confidence: 0.8920642

00:13:36.837 --> 00:13:38.988 interim analysis looks at the data

NOTE Confidence: 0.8920642

00:13:38.988 --> 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 --> 00:13:45.490 there's any chance chance of success.

NOTE Confidence: 0.8920642

00:13:45.490 --> 00:13:48.154 And the futility analysis indicated that

NOTE Confidence: 0.8920642

00:13:48.154 --> 00:13:51.755 that they were in fact futile and the

NOTE Confidence: 0.8920642

00:13:51.755 --> 00:13:54.634 studies were stopped and and all the

NOTE Confidence: 0.8920642

00:13:54.634 --> 00:13:56.589 participants were brought in termination.

NOTE Confidence: 0.8920642

00:13:56.590 --> 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 --> 00:14:04.050 the futility analysis because

NOTE Confidence: 0.8920642

00:14:04.050 --> 00:14:06.430 when all the data came in,

NOTE Confidence: 0.8920642

00:14:06.430 --> 00:14:07.555 and particularly there,

NOTE Confidence: 0.8920642

00:14:07.555 --> 00:14:10.180 there were three more months that had

NOTE Confidence: 0.8920642

00:14:10.250 --> 00:14:12.562 elapsed from the data cut point to the

NOTE Confidence: 0.8920642

00:14:12.562 --> 00:14:15.178 time all the data stopped being gathered.

NOTE Confidence: 0.8920642

00:14:15.180 --> 00:14:18.237 And and and obviously emerge will

NOTE Confidence: 0.8920642

00:14:18.237 --> 00:14:21.459 emerge emerged as a positive study.

NOTE Confidence: 0.8920642

00:14:21.460 --> 00:14:24.452 So and and without going into all of

NOTE Confidence: 0.8920642

00:14:24.452 --> 00:14:27.465 the the reasons why the BIOSTATISTICIANS

NOTE Confidence: 0.8920642

00:14:27.465 --> 00:14:31.160 messed up which they which they did.

NOTE Confidence: 0.8920642

00:14:31.160 --> 00:14:33.146 There is yet another thing that

NOTE Confidence: 0.8920642

00:14:33.146 --> 00:14:35.451 happened to these studies that was very

NOTE Confidence: 0.8920642

00:14:35.451 --> 00:14:37.380 unfortunate and that is that Biogen

NOTE Confidence: 0.8920642

00:14:37.380 --> 00:14:39.780 determined that the dosing they were

NOTE Confidence: 0.8920642

00:14:39.780 --> 00:14:42.542 using for the studies was really not

NOTE Confidence: 0.8920642

00:14:42.542 --> 00:14:45.550 not optimal and actually did a midstream.

NOTE Confidence: 0.8920642

00:14:45.550 --> 00:14:46.798 Changing of dose.

NOTE Confidence: 0.8920642

00:14:46.798 --> 00:14:49.294 And with that involved is originally

NOTE Confidence: 0.8920642

00:14:49.294 --> 00:14:51.968 they had not felt everybody could

NOTE Confidence: 0.8920642

00:14:51.968 --> 00:14:54.153 safely tolerate the high relevant

NOTE Confidence: 0.8920642

00:14:54.227 --> 00:14:55.919 dose of 10 megs per kig.

NOTE Confidence: 0.8920642

00:14:55.920 --> 00:14:58.594 That's the dark blue in this figure.

NOTE Confidence: 0.8920642

00:14:58.600 --> 00:14:58.892 So,

NOTE Confidence: 0.8920642

00:14:58.892 --> 00:15:01.884 so a lot of people who carry the APOE 4

NOTE Confidence: 0.8920642

00:15:01.884 --> 00:15:04.870 gene were only going up to six megs per keg,

NOTE Confidence: 0.8920642

00:15:04.870 --> 00:15:05.994 which is, you know,

NOTE Confidence: 0.8920642

00:15:05.994 --> 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 --> 00:15:08.911 subtherapeutic.

NOTE Confidence: 0.8920642

00:15:08.911 --> 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 --> 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 --> 00:15:24.317 dose arm of the study and only those

NOTE Confidence: 0.8920642

00:15:24.317 --> 00:15:26.647 people assigned to active treatment,

NOTE Confidence: 0.8920642

00:15:26.650 --> 00:15:27.686 not placebo.

NOTE Confidence: 0.8920642

00:15:27.686 --> 00:15:31.312 So what you really wanna see here

NOTE Confidence: 0.8920642

00:15:31.312 --> 00:15:34.048 is that from 24 weeks onward,

NOTE Confidence: 0.8920642

00:15:34.048 --> 00:15:36.750 they should just be all dark blue.

NOTE Confidence: 0.8920642

00:15:36.750 --> 00:15:37.730 That would be the ideal.

NOTE Confidence: 0.8920642

00:15:37.730 --> 00:15:39.486 Apart from early discontinuations,

NOTE Confidence: 0.8920642

00:15:39.486 --> 00:15:43.188 it should just be a sea of dark blue.

NOTE Confidence: 0.8920642

00:15:43.190 --> 00:15:45.140 But it's not.

NOTE Confidence: 0.8920642

00:15:45.140 --> 00:15:46.196 The yellow, you know,

NOTE Confidence: 0.8920642

00:15:46.196 --> 00:15:47.780 a lot of people who who,

NOTE Confidence: 0.8920642

00:15:47.780 --> 00:15:49.604 you know were early terminated for

NOTE Confidence: 0.8920642

00:15:49.604 --> 00:15:51.548 futility and all of these lighter

NOTE Confidence: 0.8920642

00:15:51.548 --> 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 --> 00:15:55.922 mucking around with subtherapeutic

NOTE Confidence: 0.8920642

00:15:55.922 --> 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 --> 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 --> 00:16:07.562 is that this differentially impacted

NOTE Confidence: 0.8920642

00:16:07.562 --> 00:16:10.717 the two studies because in emerge

NOTE Confidence: 0.8920642

00:16:10.720 --> 00:16:13.072 29% of people receive the full

NOTE Confidence: 0.8920642

00:16:13.072 --> 00:16:15.490 complement of the 10 milligram.

NOTE Confidence: 0.8920642

00:16:15.490 --> 00:16:18.521 Kilogram doses and engage only 22%.

NOTE Confidence: 0.8920642

00:16:18.521 --> 00:16:20.849 Did you know is that a big difference

NOTE Confidence: 0.8920642

00:16:20.849 --> 00:16:23.106 this had to do with the fact that

NOTE Confidence: 0.8920642

00:16:23.106 --> 00:16:24.972 that engage was an earlier timeline

NOTE Confidence: 0.8920642

00:16:24.972 --> 00:16:26.940 study and so it didn't benefit

NOTE Confidence: 0.8920642

00:16:26.940 --> 00:16:28.866 as much from the modifications.

NOTE Confidence: 0.8920642

00:16:28.866 --> 00:16:31.260 But in any case the argument

NOTE Confidence: 0.847965362777778

00:16:31.330 --> 00:16:32.990 Biogen really tried to make

NOTE Confidence: 0.847965362777778

00:16:32.990 --> 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 --> 00:16:39.244 agreed was that if you just looked

NOTE Confidence: 0.847965362777778

00:16:39.244 --> 00:16:41.467 at people who received the full

NOTE Confidence: 0.847965362777778

00:16:41.467 --> 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 benefit.

NOTE Confidence: 0.847965362777778

00:16:45.650 --> 00:16:47.468 Unfortunately that's not how it works.

NOTE Confidence: 0.847965362777778

00:16:47.470 --> 00:16:49.290 When you talk about a phase three

NOTE Confidence: 0.847965362777778

00:16:49.290 --> 00:16:50.479 registration trial with the FDA,

NOTE Confidence: 0.847965362777778

00:16:50.480 --> 00:16:51.800 you don't get to do these

NOTE Confidence: 0.847965362777778

00:16:51.800 --> 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 --> 00:16:56.668 you've got to pre specify and

NOTE Confidence: 0.847965362777778

00:16:56.668 --> 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 --> 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 --> 00:17:13.192 June of 21 via the accelerated

NOTE Confidence: 0.847965362777778

00:17:13.192 --> 00:17:15.830 pathway based on the biomarker.

NOTE Confidence: 0.847965362777778

00:17:15.830 --> 00:17:16.910 That was unvalidated.

NOTE Confidence: 0.847965362777778

00:17:16.910 --> 00:17:19.987 You know to that point this was completely

NOTE Confidence: 0.847965362777778

00:17:19.987 --> 00:17:22.885 against the recommendation of the FDA

NOTE Confidence: 0.847965362777778

00:17:22.885 --> 00:17:25.599 Advisory Committee who voted 8 to one

NOTE Confidence: 0.847965362777778

00:17:25.599 --> 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 --> 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 --> 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 --> 00:17:44.128 and they indicate they're only

NOTE Confidence: 0.847965362777778

00:17:44.128 --> 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 --> 00:17:47.564 full traditional approval

NOTE Confidence: 0.847965362777778

00:17:47.564 --> 00:17:49.288 based on clinical measures,

NOTE Confidence: 0.847965362777778

00:17:49.290 --> 00:17:51.660 not biomarkers and only under in

NOTE Confidence: 0.847965362777778

00:17:51.660 --> 00:17:54.708 in in a research context coverage

NOTE Confidence: 0.847965362777778

00:17:54.708 --> 00:17:56.787 with evidence development.

NOTE Confidence: 0.847965362777778

00:17:56.790 --> 00:17:59.480 So that's where that stood.

NOTE Confidence: 0.847965362777778

00:17:59.480 --> 00:18:01.850 And you know Biogen then subsequently

NOTE Confidence: 0.847965362777778

00:18:01.850 --> 00:18:04.259 you know launched yet another study

NOTE Confidence: 0.847965362777778

00:18:04.259 --> 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 --> 00:18:12.156 this is the attempt to have a second

NOTE Confidence: 0.847965362777778

00:18:12.156 --> 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 --> 00:18:23.374 attempt to have a redo on on full

NOTE Confidence: 0.847965362777778

00:18:23.374 --> 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 --> 00:18:29.559 launch it fairly rapidly.

NOTE Confidence: 0.847965362777778

00:18:29.560 --> 00:18:32.233 And then at the end of this past year,

NOTE Confidence: 0.847965362777778

00:18:32.240 --> 00:18:33.920 many of you may have seen that

NOTE Confidence: 0.847965362777778

00:18:33.920 --> 00:18:35.899 there was a congressional report.

NOTE Confidence: 0.847965362777778

00:18:35.900 --> 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 --> 00:18:45.507 we're really investigated including

NOTE Confidence: 0.847965362777778

00:18:45.507 --> 00:18:47.842 that there was this unusual

NOTE Confidence: 0.847965362777778

00:18:47.842 --> 00:18:50.245 collaborative work stream where FDA

NOTE Confidence: 0.847965362777778

00:18:50.245 --> 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 --> 00:18:56.349 mutually.

NOTE Confidence: 0.889060043333333

00:18:58.540 --> 00:19:01.144 All right. Well, and so it was

NOTE Confidence: 0.889060043333333

00:19:01.144 --> 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 --> 00:19:13.920 amab appeared actually to meet

NOTE Confidence: 0.889060043333333

00:19:14.003 --> 00:19:16.427 the bar for for full approval.

NOTE Confidence: 0.889060043333333

00:19:16.430 --> 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 --> 00:19:23.470 fully presented at the end of November

NOTE Confidence: 0.889060043333333

00:19:23.470 --> 00:19:26.289 and appeared online in the New England

NOTE Confidence: 0.889060043333333

00:19:26.289 --> 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 --> 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 --> 00:19:36.565 this publication you know and

NOTE Confidence: 0.889060043333333

00:19:36.565 --> 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 --> 00:19:44.708 this is a a busy slide.

NOTE Confidence: 0.72081560625

00:19:44.710 --> 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 --> 00:19:57.798 It's selectively binds to

NOTE Confidence: 0.72081560625

00:19:57.798 --> 00:19:59.910 soluble aggregated species,

NOTE Confidence: 0.72081560625

00:19:59.910 --> 00:20:02.310 you know oligomers and proto fibrils.

NOTE Confidence: 0.72081560625

00:20:02.310 --> 00:20:05.810 It's got 1000 fold selectivity for those

NOTE Confidence: 0.72081560625

00:20:05.810 --> 00:20:08.493 species over monomers and it even has

00:20:08.493 --> 00:20:10.026 a tenfold selectivity over fibrils.

00:20:10.026 --> 00:20:12.540 That are in plaque so that we know it.

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

00:20:14.640 --> 00:20:18.648 it clears amyloid plaque on a PET scan.

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

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

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

00:20:27.840 --> 00:20:30.150 clarity on which is that I'm only

00:20:30.150 --> 00:20:32.128 going to show you one study,

00:20:32.130 --> 00:20:33.618 I'm not going to show you

00:20:33.618 --> 00:20:34.610 two studies right now.

00:20:34.610 --> 00:20:35.870 Why is that?

00:20:35.870 --> 00:20:38.810 And it's because in this case you

00:20:38.905 --> 00:20:41.360 know the Canada went through very

00:20:41.360 --> 00:20:43.853 extensive phase two testing and their

NOTE Confidence: 0.72081560625

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

NOTE Confidence: 0.72081560625

00:20:46.587 --> 00:20:49.506 people which was actually a positive study.

NOTE Confidence: 0.72081560625

00:20:49.510 --> 00:20:52.598 Still not a registration trial and so it

NOTE Confidence: 0.72081560625

00:20:52.598 --> 00:20:55.558 was accepted as as a first positive study.

NOTE Confidence: 0.72081560625

00:20:55.560 --> 00:20:57.474 So in this case the cannonade

NOTE Confidence: 0.72081560625

00:20:57.474 --> 00:20:59.422 really needed to confirm that with

NOTE Confidence: 0.72081560625

00:20:59.422 --> 00:21:01.234 with a single large phase three

NOTE Confidence: 0.72081560625

00:21:01.234 --> 00:21:03.258 trial and that that's the reason.

NOTE Confidence: 0.72081560625

00:21:03.260 --> 00:21:06.748 So in this study you can see that

NOTE Confidence: 0.72081560625

00:21:06.748 --> 00:21:10.196 there were 1795 people who were

NOTE Confidence: 0.72081560625

00:21:10.196 --> 00:21:12.772 randomized with early Alzheimer's

NOTE Confidence: 0.72081560625

00:21:12.772 --> 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 --> 00:21:26.010 they had to be confirmed for Alzheimer's

NOTE Confidence: 0.72081560625

00:21:26.010 --> 00:21:29.200 pathogenesis by any amyloid PET scan.

NOTE Confidence: 0.72081560625

00:21:29.200 --> 00:21:31.600 They were randomized 1 to one

NOTE Confidence: 0.72081560625

00:21:31.600 --> 00:21:34.180 to either like cannab or placebo

NOTE Confidence: 0.72081560625

00:21:34.180 --> 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 --> 00:21:41.305 So this is administered twice

NOTE Confidence: 0.72081560625

00:21:41.305 --> 00:21:44.570 as often as that you can amount.

NOTE Confidence: 0.72081560625

00:21:44.570 --> 00:21:47.138 And that was an 18 month trial and

NOTE Confidence: 0.72081560625

00:21:47.138 --> 00:21:50.052 that at the end of that you know there

NOTE Confidence: 0.72081560625

00:21:50.052 --> 00:21:52.453 is an open extension trial which

NOTE Confidence: 0.72081560625

00:21:52.453 --> 00:21:55.262 is very much ongoing and that means

NOTE Confidence: 0.72081560625

00:21:55.262 --> 00:21:58.430 everybody in in this phase is on active drug,

NOTE Confidence: 0.72081560625

00:21:58.430 --> 00:22:00.758 no more placebo 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 --> 00:22:05.583 cover the extension phase at all.

NOTE Confidence: 0.72081560625

00:22:05.590 --> 00:22:07.438 I'm only going to mention it when

NOTE Confidence: 0.72081560625

00:22:07.438 --> 00:22:09.880 it comes to some of the you know

NOTE Confidence: 0.72081560625

00:22:09.880 --> 00:22:11.830 publicized you know safety issues that

NOTE Confidence: 0.72081560625

00:22:11.830 --> 00:22:13.937 have come up in the extension phase.

NOTE Confidence: 0.72081560625

00:22:13.940 --> 00:22:16.350 And on the far right,

NOTE Confidence: 0.72081560625

00:22:16.350 --> 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 --> 00:22:24.118 individually over the next few slides.

NOTE Confidence: 0.87420221

00:22:26.640 --> 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 --> 00:22:39.358 So meaning that before we got to the 17195

NOTE Confidence: 0.87420221

00:22:39.358 --> 00:22:41.686 people who were randomized and treated,

NOTE Confidence: 0.87420221

00:22:41.690 --> 00:22:44.910 there were nearly 6000 who were screened.

NOTE Confidence: 0.87420221

00:22:44.910 --> 00:22:47.558 Most of them were not eligible for the

NOTE Confidence: 0.87420221

00:22:47.558 --> 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 --> 00:22:58.194 pat or even more commonly that they

NOTE Confidence: 0.87420221

00:22:58.194 --> 00:23:00.456 weren't quite in the right cognitive

NOTE Confidence: 0.87420221

00:23:00.456 --> 00:23:02.630 range for this early ad study.

NOTE Confidence: 0.87420221

00:23:02.630 --> 00:23:05.134 But in any case.

NOTE Confidence: 0.87420221

00:23:05.134 --> 00:23:07.914 The 1795 who are randomized and treated

NOTE Confidence: 0.87420221

00:23:07.914 --> 00:23:09.773 were then evenly divided between

NOTE Confidence: 0.87420221

00:23:09.773 --> 00:23:11.927 the placebo and the lucama groups.

NOTE Confidence: 0.87420221

00:23:11.930 --> 00:23:16.140 And in the placebo group 84.4 completed

NOTE Confidence: 0.87420221

00:23:16.140 --> 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 --> 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 --> 00:23:27.974 more adverse events you know as

NOTE Confidence: 0.87420221

00:23:27.974 --> 00:23:32.392 shown in in these boxes and the the

NOTE Confidence: 0.87420221

00:23:32.392 --> 00:23:34.562 populations of analysis are are

NOTE Confidence: 0.87420221

00:23:34.562 --> 00:23:37.486 worth you know just mentioning for

NOTE Confidence: 0.87420221

00:23:37.486 --> 00:23:40.438 for all efficacy measures we looked

NOTE Confidence: 0.87420221

00:23:40.520 --> 00:23:42.980 at what's called the modified.

NOTE Confidence: 0.87420221

00:23:42.980 --> 00:23:44.636 Intent to treat population.

NOTE Confidence: 0.87420221

00:23:44.636 --> 00:23:48.517 And all that means is you have to have

NOTE Confidence: 0.87420221

00:23:48.517 --> 00:23:50.707 somebody 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 --> 00:24:01.260 not everybody gets dosed gets there.

NOTE Confidence: 0.87420221

00:24:01.260 --> 00:24:03.297 They might have had to terminate early,

NOTE Confidence: 0.87420221

00:24:03.300 --> 00:24:04.770 you know for a side effect and

NOTE Confidence: 0.87420221

00:24:04.770 --> 00:24:06.500 never had a follow-up assessment.

NOTE Confidence: 0.87420221

00:24:06.500 --> 00:24:08.930 So that's the population used

NOTE Confidence: 0.87420221

00:24:08.930 --> 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 --> 00:24:15.756 randomized and dosed.

NOTE Confidence: 0.8517360675

00:24:18.520 --> 00:24:22.150 Now here are the baseline

NOTE Confidence: 0.8517360675

00:24:22.150 --> 00:24:25.392 characteristics of the 1795 people.

NOTE Confidence: 0.8517360675

00:24:25.392 --> 00:24:29.120 As you can see, this was a global study,

NOTE Confidence: 0.8517360675

00:24:29.120 --> 00:24:31.464 although a majority of them were in the

NOTE Confidence: 0.8517360675

00:24:31.464 --> 00:24:33.789 far right column in the United States.

NOTE Confidence: 0.8517360675

00:24:33.790 --> 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 --> 00:24:42.534 I think 20% were underage 65

NOTE Confidence: 0.8517360675

00:24:42.534 --> 00:24:48.910 and close to 15% were over 80.

NOTE Confidence: 0.8517360675

00:24:48.910 --> 00:24:51.694 The other thing of note here I want

NOTE Confidence: 0.8517360675

00:24:51.694 --> 00:24:54.789 to call attention to is race and

NOTE Confidence: 0.8517360675

00:24:54.789 --> 00:24:57.531 ethnicity and and that's because in

NOTE Confidence: 0.8517360675

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

NOTE Confidence: 0.8517360675

00:24:59.967 --> 00:25:03.184 job of including populations that

NOTE Confidence: 0.8517360675

00:25:03.184 --> 00:25:07.374 represent the United States population.

NOTE Confidence: 0.8517360675

00:25:07.380 --> 00:25:09.949 It's a it's a really, really important thing.

NOTE Confidence: 0.8517360675

00:25:09.949 --> 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 --> 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 --> 00:25:28.102 That's good for us,

NOTE Confidence: 0.8517360675

00:25:28.102 --> 00:25:29.717 but it's it's woefully inadequate.

NOTE Confidence: 0.8517360675

00:25:29.720 --> 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 --> 00:25:37.899 seniors in the United States with.

NOTE Confidence: 0.8517360675

00:25:37.900 --> 00:25:39.072 Hispanic ethnicity,

NOTE Confidence: 0.8517360675

00:25:39.072 --> 00:25:42.540 we actually did well, this is,

NOTE Confidence: 0.8517360675

00:25:42.540 --> 00:25:46.271 this is really good 22.5% because that

NOTE Confidence: 0.8517360675

00:25:46.271 --> 00:25:48.756 actually over represents Hispanics who,

NOTE Confidence: 0.8517360675

00:25:48.760 --> 00:25:51.539 who in the senior senior age groups

NOTE Confidence: 0.8517360675

00:25:51.539 --> 00:25:54.396 would again be in the order of 10%.

NOTE Confidence: 0.8517360675

00:25:54.400 --> 00:25:56.885 But we still need to do better

NOTE Confidence: 0.8517360675

00:25:56.885 --> 00:25:59.389 and it's an important issue.

NOTE Confidence: 0.8517360675

00:25:59.390 --> 00:26:01.134 With regard to other

NOTE Confidence: 0.8517360675

00:26:01.134 --> 00:26:02.006 clinical characteristics,

NOTE Confidence: 0.8517360675

00:26:02.010 --> 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 --> 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 --> 00:26:11.776 more MCI prodromal than they are dementia.

NOTE Confidence: 0.8517360675

00:26:11.780 --> 00:26:13.761 Most of these people are are functionally

NOTE Confidence: 0.8517360675

00:26:13.761 --> 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 --> 00:26:19.620 who do their own finances,

NOTE Confidence: 0.8517360675

00:26:19.620 --> 00:26:22.020 who do cooking, manage their meds,

NOTE Confidence: 0.8517360675

00:26:22.020 --> 00:26:24.100 that's the majority of people.

NOTE Confidence: 0.8517360675

00:26:24.100 --> 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 --> 00:26:28.597 although it includes some with

NOTE Confidence: 0.8517360675

00:26:28.597 --> 00:26:31.140 you know very mild dementia.

NOTE Confidence: 0.8517360675

00:26:31.140 --> 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 --> 00:26:35.350 For those of you not familiar,

NOTE Confidence: 0.8517360675

00:26:35.350 --> 00:26:37.653 April 4 is the major genetic risk

NOTE Confidence: 0.8517360675

00:26:37.653 --> 00:26:39.170 factor for Alzheimer's disease.

NOTE Confidence: 0.8517360675

00:26:39.170 --> 00:26:43.640 You know, late onset Alzheimer's and.

NOTE Confidence: 0.8517360675

00:26:43.640 --> 00:26:48.232 And typically about 69% of all the

NOTE Confidence: 0.8517360675

00:26:48.232 --> 00:26:50.440 participants carried the April 4 at

NOTE Confidence: 0.8517360675

00:26:50.519 --> 00:26:53.144 least one copy apply 4 allele that

NOTE Confidence: 0.8517360675

00:26:53.144 --> 00:26:55.279 that compares to about maybe 15

NOTE Confidence: 0.8517360675

00:26:55.279 --> 00:26:57.200 to 20% in the general population.

NOTE Confidence: 0.8517360675

00:26:57.200 --> 00:26:59.749 This is a very typical sample in this

NOTE Confidence: 0.8517360675

00:26:59.749 --> 00:27:02.240 regard and we see that percent for you know,

NOTE Confidence: 0.8517360675

00:27:02.240 --> 00:27:05.840 people who carry one copy versus.

NOTE Confidence: 0.8517360675

00:27:05.840 --> 00:27:07.470 2 copies of the homozygotes,

NOTE Confidence: 0.8517360675

00:27:07.470 --> 00:27:09.402 homozygotes for about

NOTE Confidence: 0.8517360675

00:27:09.402 --> 00:27:11.978 15.5% of the population.

NOTE Confidence: 0.8517360675

00:27:11.980 --> 00:27:13.140 And this is important,

NOTE Confidence: 0.8517360675

00:27:13.140 --> 00:27:13.720 you know,

NOTE Confidence: 0.8517360675

00:27:13.720 --> 00:27:14.767 as we'll see,

NOTE Confidence: 0.8517360675

00:27:14.767 --> 00:27:16.163 particularly as it relates

NOTE Confidence: 0.8517360675

00:27:16.163 --> 00:27:18.519 to some of the safety issues,

NOTE Confidence: 0.8517360675

00:27:18.520 --> 00:27:21.664 about a little more than half of people

NOTE Confidence: 0.8517360675

00:27:21.664 --> 00:27:25.017 were on an approved Alzheimer's drug

NOTE Confidence: 0.8517360675

00:27:25.017 --> 00:27:28.731 like a cholinesterase 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 --> 00:27:34.290 The top line efficacy

NOTE Confidence: 0.8517360675

00:27:34.290 --> 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 --> 00:27:41.289 just what it was for aducanumab,

NOTE Confidence: 0.8517360675

00:27:41.290 --> 00:27:43.585 it's the change from baseline

NOTE Confidence: 0.8517360675

00:27:43.585 --> 00:27:46.630 at 18 months in the Cdr SB.

NOTE Confidence: 0.8517360675

00:27:46.630 --> 00:27:48.716 I'm also going to show you most

NOTE Confidence: 0.8517360675

00:27:48.716 --> 00:27:50.604 of the key secondary endpoints

NOTE Confidence: 0.8517360675

00:27:50.604 --> 00:27:52.448 shown on the right,

NOTE Confidence: 0.8517360675

00:27:52.450 --> 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 --> 00:27:58.982 scan and then clinical measures.

NOTE Confidence: 0.785593378461538

00:27:58.982 --> 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 --> 00:28:03.678 adcoms for the sake of time.

NOTE Confidence: 0.785593378461538

00:28:03.680 --> 00:28:05.920 I'm going to show you the pure cognitive

NOTE Confidence: 0.785593378461538

00:28:05.920 --> 00:28:07.350 and functional measures though.

NOTE Confidence: 0.850666078636364

00:28:09.820 --> 00:28:12.220 So, so this is perhaps you know really

NOTE Confidence: 0.850666078636364

00:28:12.220 --> 00:28:15.455 the key slide you know of of the whole

NOTE Confidence: 0.850666078636364

00:28:15.455 --> 00:28:17.339 presentation regarding we can't amab,

NOTE Confidence: 0.850666078636364

00:28:17.340 --> 00:28:20.094 you know these are the results for the the,

NOTE Confidence: 0.850666078636364

00:28:20.100 --> 00:28:23.268 the primary outcome, the primary endpoint.

NOTE Confidence: 0.850666078636364

00:28:23.270 --> 00:28:26.230 This is what makes it a positive study.

NOTE Confidence: 0.850666078636364

00:28:26.230 --> 00:28:30.251 The CD RSB and you know this is

NOTE Confidence: 0.850666078636364

00:28:30.251 --> 00:28:33.264 this is similar to what we saw for

NOTE Confidence: 0.850666078636364

00:28:33.264 --> 00:28:35.776 aducanumab in emerge and engage except

NOTE Confidence: 0.850666078636364

00:28:35.776 --> 00:28:38.746 you'll remember that that you know

44

NOTE Confidence: 0.850666078636364

00:28:38.746 --> 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 --> 00:28:46.809 down is being bad and we we did that

NOTE Confidence: 0.850666078636364

00:28:46.809 --> 00:28:49.068 because that way you could look at

NOTE Confidence: 0.850666078636364

00:28:49.068 --> 00:28:51.336 all the slides I looked at all the

NOTE Confidence: 0.850666078636364

00:28:51.336 --> 00:28:53.162 figures in the study and down was

NOTE Confidence: 0.850666078636364

00:28:53.162 --> 00:28:55.146 always bad but in any case that's how

NOTE Confidence: 0.850666078636364

00:28:55.146 --> 00:28:57.019 it's graphed and what you can see.

NOTE Confidence: 0.850666078636364

00:28:57.020 --> 00:29:00.092 Is that the placebo group worsens

NOTE Confidence: 0.850666078636364

00:29:00.092 --> 00:29:02.750 by 1.66 points over 18 months.

NOTE Confidence: 0.850666078636364

00:29:02.750 --> 00:29:04.928 Not quite as much as in the end you

NOTE Confidence: 0.850666078636364

00:29:04.928 --> 00:29:07.235 can't map studies and the treated group.

NOTE Confidence: 0.847906556

00:29:11.140 --> 00:29:14.576 1.22 with a difference of 0.45 and

NOTE Confidence: 0.847906556

00:29:14.576 --> 00:29:17.066 which is highly highly statistically

NOTE Confidence: 0.847906556

00:29:17.066 --> 00:29:20.085 significant and it represents a 27%

NOTE Confidence: 0.847906556

00:29:20.085 --> 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 --> 00:29:29.317 as early as six months and they at

NOTE Confidence: 0.847906556

00:29:29.317 --> 00:29:31.570 least numerically widen. Thereafter.

NOTE Confidence: 0.88777143

00:29:33.760 --> 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 --> 00:29:40.288 but I wanted to to show this in

NOTE Confidence: 0.88777143

00:29:40.288 --> 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 --> 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 --> 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 --> 00:29:55.308 but are they meaningful.

NOTE Confidence: 0.88777143

00:29:55.308 --> 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

NOTE Confidence: 0.88777143

00:29:59.453 --> 00:30:01.984 that at least I think about the

NOTE Confidence: 0.88777143

00:30:01.984 --> 00:30:03.556 meaningfulness of the results.

NOTE Confidence: 0.88777143

00:30:03.560 --> 00:30:05.926 And one way that I would commonly

NOTE Confidence: 0.88777143

00:30:05.926 --> 00:30:08.930 explain to A to a patient or participant

NOTE Confidence: 0.88777143

00:30:08.930 --> 00:30:11.825 is what's shown here and it has to

NOTE Confidence: 0.88777143

00:30:11.825 --> 00:30:13.932 do with kind of a time savings.

NOTE Confidence: 0.88777143

00:30:13.940 --> 00:30:17.268 So that is that in the placebo group

NOTE Confidence: 0.88777143

00:30:17.268 --> 00:30:19.526 the amount of deterioration that

NOTE Confidence: 0.88777143

00:30:19.526 --> 00:30:23.340 occurs at end of study at 18 months.

NOTE Confidence: 0.88777143

00:30:23.340 --> 00:30:25.698 If the rates of decline continued

NOTE Confidence: 0.88777143

00:30:25.698 --> 00:30:28.803 after 18 months as they as they are

NOTE Confidence: 0.88777143

00:30:28.803 --> 00:30:31.427 to that point and that's that's an

NOTE Confidence: 0.88777143

00:30:31.427 --> 00:30:34.003 if that's a that's a big assumption.

NOTE Confidence: 0.88777143

00:30:34.010 --> 00:30:35.314 The actively treated groups

NOTE Confidence: 0.88777143

00:30:35.314 --> 00:30:37.270 will get to the same point,

NOTE Confidence: 0.88777143

00:30:37.270 --> 00:30:39.790 but they will get there about

NOTE Confidence: 0.88777143

00:30:39.790 --> 00:30:41.190 7 1/2 months later.

NOTE Confidence: 0.88777143

00:30:41.190 --> 00:30:44.030 So in that sense it's like a 7 1/2

NOTE Confidence: 0.88777143

00:30:44.030 --> 00:30:46.350 month time saving of a certain level of,

NOTE Confidence: 0.88777143

00:30:46.350 --> 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 --> 00:30:52.726 A more conservative way by the way

NOTE Confidence: 0.88777143

00:30:52.726 --> 00:30:54.949 than extrapolating is to interpolate.

NOTE Confidence: 0.88777143

00:30:54.950 --> 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 --> 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 --> 00:31:06.086 get to the point where the lucama

NOTE Confidence: 0.88777143

00:31:06.086 --> 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 --> 00:31:12.134 So that would be a more conservative,

NOTE Confidence: 0.88777143

00:31:12.140 --> 00:31:14.150 you know estimate and probably maybe

NOTE Confidence: 0.88777143

00:31:14.150 --> 00:31:16.400 the truth is somewhere in between one.

NOTE Confidence: 0.88777143

00:31:16.400 --> 00:31:18.476 One thing that's very clear though

NOTE Confidence: 0.88777143

00:31:18.476 --> 00:31:20.130 is that this kind of.

NOTE Confidence: 0.88777143

00:31:20.130 --> 00:31:22.622 Measure is very much related to how

NOTE Confidence: 0.88777143

00:31:22.622 --> 00:31:24.723 long you're on the drug, right.

NOTE Confidence: 0.88777143

00:31:24.723 --> 00:31:27.227 So and as we'll see at the very

NOTE Confidence: 0.88777143

00:31:27.227 --> 00:31:29.188 end of this presentation,

NOTE Confidence: 0.88777143

00:31:29.190 --> 00:31:31.493 you know we start to think about

NOTE Confidence: 0.88777143

00:31:31.493 --> 00:31:33.288 treating people earlier and for many

NOTE Confidence: 0.88777143

00:31:33.288 --> 00:31:35.402 years we may be able to think about

NOTE Confidence: 0.88777143

00:31:35.402 --> 00:31:37.663 much bigger effects than any of these.

NOTE Confidence: 0.88777143

00:31:37.670 --> 00:31:41.390 But you know this is this is a

NOTE Confidence: 0.88777143

00:31:41.390 --> 00:31:44.860 speculation now we're back to real data.

NOTE Confidence: 0.88777143

00:31:44.860 --> 00:31:46.855 And now I'm moving on to the

NOTE Confidence: 0.88777143

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

NOTE Confidence: 0.88777143

00:31:47.710 --> 00:31:52.176 starting with the the biomarker amyloid pet.

NOTE Confidence: 0.88777143

00:31:52.180 --> 00:31:55.246 So just as we saw with aducanumab,

NOTE Confidence: 0.88777143

00:31:55.250 --> 00:31:56.098 you know,

NOTE Confidence: 0.88777143

00:31:56.098 --> 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 --> 00:32:02.711 the same is true with lacanada here

NOTE Confidence: 0.88777143

00:32:02.711 --> 00:32:06.615 in the 18 month study you can see

NOTE Confidence: 0.88777143

00:32:06.615 --> 00:32:09.105 that people in the placebo group

NOTE Confidence: 0.88777143

00:32:09.105 --> 00:32:12.512 had you know at least a little

NOTE Confidence: 0.88777143

00:32:12.512 --> 00:32:15.230 numerical increase in amyloid binding,

NOTE Confidence: 0.88777143

00:32:15.230 --> 00:32:17.560 whereas those on the kinomap,

NOTE Confidence: 0.88777143

00:32:17.560 --> 00:32:21.100 you know steadily decreased.

NOTE Confidence: 0.88777143

00:32:21.100 --> 00:32:23.186 There is the scale that I'm not

NOTE Confidence: 0.88777143

00:32:23.186 --> 00:32:25.384 going to explain to you called a

NOTE Confidence: 0.88777143

00:32:25.384 --> 00:32:27.244 centroid scale that is being used.

NOTE Confidence: 0.88777143

00:32:27.250 --> 00:32:29.308 This is a way of standardizing you

NOTE Confidence: 0.88777143

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

NOTE Confidence: 0.88777143

00:32:31.460 --> 00:32:34.044 across scanners, across radiopharmaceuticals.

NOTE Confidence: 0.88777143

00:32:34.044 --> 00:32:38.361 But suffice it to say that you

NOTE Confidence: 0.88777143

00:32:38.361 --> 00:32:40.566 know the drug placebo 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 --> 00:32:45.745 significant but but to make to

NOTE Confidence: 0.88777143

00:32:45.745 --> 00:32:48.212 to talk a little bit about what

NOTE Confidence: 0.88777143

00:32:48.212 --> 00:32:50.417 what center Lloyd's you know.

NOTE Confidence: 0.860418372222222

00:32:50.420 --> 00:32:50.918 Represent.

NOTE Confidence: 0.860418372222222

00:32:50.918 --> 00:32:54.902 Note that at the start of the study,

NOTE Confidence: 0.860418372222222

00:32:54.910 --> 00:32:59.240 people averaged about 76 centroids.

NOTE Confidence: 0.860418372222222

00:32:59.240 --> 00:33:02.480 Note also that to get into the study,

NOTE Confidence: 0.860418372222222

00:33:02.480 --> 00:33:05.390 the threshold of positivity was

NOTE Confidence: 0.860418372222222

00:33:05.390 --> 00:33:07.358 probably about $0.30 Lloyds.

NOTE Confidence: 0.860418372222222

00:33:07.358 --> 00:33:10.151 And then note finally that at the

NOTE Confidence: 0.860418372222222

00:33:10.151 --> 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 --> 00:33:18.176 Most of them had normal scans,

NOTE Confidence: 0.860418372222222

00:33:18.180 --> 00:33:19.705 you know, visually and quantitatively

NOTE Confidence: 0.860418372222222

00:33:19.705 --> 00:33:21.620 at the end of the study.

NOTE Confidence: 0.860418372222222

00:33:21.620 --> 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 --> 00:33:25.786 as early as the very first

NOTE Confidence: 0.860418372222222

00:33:25.786 --> 00:33:27.310 pet scan at three months.

NOTE Confidence: 0.826227491111111

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

NOTE Confidence: 0.826227491111111

00:33:30.884 --> 00:33:32.972 you know to other key secondaries,

NOTE Confidence: 0.826227491111111

00:33:32.980 --> 00:33:34.900 this is the pure cognitive measure,

NOTE Confidence: 0.826227491111111

00:33:34.900 --> 00:33:39.060 the 8 US cog which is scored zero to 90.

NOTE Confidence: 0.826227491111111

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

NOTE Confidence: 0.826227491111111

00:33:41.820 --> 00:33:45.429 And what you can see here is that at

00:33:45.429 --> 00:33:49.592 the end of the 18 months the drug

00:33:49.592 --> 00:33:52.280 placebo difference was 1.44 points

00:33:52.280 --> 00:33:55.720 between drug and placebo, again highly,

00:33:55.720 --> 00:33:58.665 highly significant representing a 26%.

00:33:58.665 --> 00:34:01.935 Slowing of decline and and significant

00:34:01.935 --> 00:34:04.418 differences were evident again as

00:34:04.418 --> 00:34:07.099 early as the six month time point.

00:34:07.100 --> 00:34:09.907 And finally, this is the pure functional

00:34:09.907 --> 00:34:11.642 measure relates to activities

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

00:34:15.340 --> 00:34:17.300 This is, excuse me,

00:34:17.300 --> 00:34:20.728 squared zero to 53.

00:34:20.730 --> 00:34:24.545 In this case lower scores are better.

00:34:24.550 --> 00:34:26.046 But we graph it,

00:34:26.046 --> 00:34:28.918 you know the same direction for ease

00:34:28.918 --> 00:34:32.030 of understanding and and what you can

NOTE Confidence: 0.826227491111111

00:34:32.030 --> 00:34:35.033 see is that the placebo group worsens

NOTE Confidence: 0.826227491111111

00:34:35.033 --> 00:34:38.417 to the tune of about 5 1/2 points.

NOTE Confidence: 0.826227491111111

00:34:38.420 --> 00:34:41.684 The actively treated about two points

NOTE Confidence: 0.826227491111111

00:34:41.684 --> 00:34:45.159 less than that highly significant in

NOTE Confidence: 0.826227491111111

00:34:45.159 --> 00:34:49.228 this case representing a 37% slowing of

NOTE Confidence: 0.826227491111111

00:34:49.228 --> 00:34:51.888 decline with the treatment differences

NOTE Confidence: 0.826227491111111

00:34:51.888 --> 00:34:55.346 again evident as early as six months.

NOTE Confidence: 0.826227491111111

00:34:55.350 --> 00:34:57.480 And with regard to clinical meaningfulness,

NOTE Confidence: 0.826227491111111

00:34:57.480 --> 00:35:00.256 I would just I find at least in

NOTE Confidence: 0.826227491111111

00:35:00.256 --> 00:35:02.997 in when people see these data,

NOTE Confidence: 0.826227491111111

00:35:03.000 --> 00:35:05.961 this is a measure that is more

NOTE Confidence: 0.826227491111111

00:35:05.961 --> 00:35:08.360 easily seen as meaningful.

NOTE Confidence: 0.826227491111111

00:35:08.360 --> 00:35:09.892 Because of what it is, right?

NOTE Confidence: 0.826227491111111

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

NOTE Confidence: 0.826227491111111

00:35:10.174 --> 00:35:12.430 these are people who mostly start the study,

54

NOTE Confidence: 0.826227491111111

00:35:12.430 --> 00:35:14.902 able to drive a car, do finances,

NOTE Confidence: 0.826227491111111

00:35:14.902 --> 00:35:18.340 you know, Cook, manage their medications.

NOTE Confidence: 0.826227491111111

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

NOTE Confidence: 0.826227491111111

00:35:22.950 --> 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: 0.826227491111111

00:35:26.568 --> 00:35:29.684 it's hard not to think of such such

NOTE Confidence: 0.826227491111111

00:35:29.684 --> 00:35:32.468 kinds of effects as as meaningful,

NOTE Confidence: 0.826227491111111

00:35:32.470 --> 00:35:33.540 you know, in real life.

NOTE Confidence: 0.846598971666667

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

NOTE Confidence: 0.846598971666667

00:35:38.916 --> 00:35:41.600 want to go on to yet another kind of measure.

NOTE Confidence: 0.846598971666667

00:35:41.600 --> 00:35:43.368 Now what I've shown you up until now

NOTE Confidence: 0.846598971666667

00:35:43.368 --> 00:35:45.040 are the top line, you know, results,

NOTE Confidence: 0.846598971666667

00:35:45.040 --> 00:35:48.680 you know, the primary and the secondary,

NOTE Confidence: 0.846598971666667

00:35:48.680 --> 00:35:50.408 but there are other, you know,

NOTE Confidence: 0.846598971666667

00:35:50.410 --> 00:35:53.164 more exploratory measures that were done

NOTE Confidence: 0.846598971666667

00:35:53.164 --> 00:35:57.386 and one of them pertains to quality of life.

NOTE Confidence: 0.846598971666667

00:35:57.390 --> 00:35:59.966 Quality of life which may not be.

NOTE Confidence: 0.846598971666667

00:35:59.970 --> 00:36:03.666 Fully measured with cognition and function,

NOTE Confidence: 0.846598971666667

00:36:03.670 --> 00:36:05.154 so in this case.

NOTE Confidence: 0.846598971666667

00:36:05.154 --> 00:36:07.009 We're looking at four different

NOTE Confidence: 0.846598971666667

00:36:07.009 --> 00:36:09.009 scales that were administered.

NOTE Confidence: 0.846598971666667

00:36:09.010 --> 00:36:12.258 The two in the top row are both

NOTE Confidence: 0.846598971666667

00:36:12.258 --> 00:36:15.423 assessed quality of life for the

NOTE Confidence: 0.846598971666667

00:36:15.423 --> 00:36:17.124 patient participant themselves.

NOTE Confidence: 0.846598971666667

00:36:17.130 --> 00:36:19.650 The two in the bottom row of for the,

NOTE Confidence: 0.846598971666667

00:36:19.650 --> 00:36:22.010 you know the caregiver partner.

NOTE Confidence: 0.846598971666667

00:36:22.010 --> 00:36:24.670 And without going into these in detail

NOTE Confidence: 0.846598971666667

00:36:24.670 --> 00:36:27.382 you know what you can see is that

NOTE Confidence: 0.846598971666667

00:36:27.382 --> 00:36:29.910 all four of them show statistically

NOTE Confidence: 0.846598971666667

00:36:29.910 --> 00:36:32.856 significant benefit you know slowing of

NOTE Confidence: 0.846598971666667

00:36:32.856 --> 00:36:35.149 decline and and just as a poster child

NOTE Confidence: 0.846598971666667

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

NOTE Confidence: 0.846598971666667

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

NOTE Confidence: 0.846598971666667

00:36:39.322 --> 00:36:43.603 Here is a a a questionnaire that asked

NOTE Confidence: 0.846598971666667

00:36:43.603 --> 00:36:46.825 questions like how happy are you?

NOTE Confidence: 0.846598971666667

00:36:46.830 --> 00:36:48.986 How are your relationships with your family,

NOTE Confidence: 0.846598971666667

00:36:48.990 --> 00:36:49.707 with your friends?

NOTE Confidence: 0.846598971666667

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

NOTE Confidence: 0.846598971666667

00:36:51.750 --> 00:36:54.410 You're you know, your your overall health.

NOTE Confidence: 0.846598971666667

00:36:54.410 --> 00:36:56.050 And on this measure,

NOTE Confidence: 0.846598971666667

00:36:56.050 --> 00:36:58.100 the Kanab is associated with

NOTE Confidence: 0.846598971666667

00:36:58.100 --> 00:36:59.860 a 56% lower decline.

NOTE Confidence: 0.846598971666667

00:36:59.860 --> 00:37:02.110 And comparison to the placebo

NOTE Confidence: 0.846598971666667

00:37:02.110 --> 00:37:04.746 group at the end of the study.

NOTE Confidence: 0.846598971666667

00:37:04.750 --> 00:37:07.350 So again for those who think no clinical

NOTE Confidence: 0.846598971666667

00:37:07.350 --> 00:37:09.289 meaningfulness in these kind of effects,

NOTE Confidence: 0.846598971666667

00:37:09.290 --> 00:37:12.093 I mean I I would I would just ask to to

NOTE Confidence: 0.846598971666667

00:37:12.093 --> 00:37:14.424 look at these these kinds of results.

NOTE Confidence: 0.92799218

00:37:18.290 --> 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 --> 00:37:26.316 And to do that I need to introduce

NOTE Confidence: 0.92799218

00:37:26.316 --> 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 --> 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 --> 00:37:40.249 a whole lot because it implies that

NOTE Confidence: 0.92799218

00:37:40.249 --> 00:37:43.610 these are only imaging abnormalities,

NOTE Confidence: 0.92799218

00:37:43.610 --> 00:37:45.410 you know, whereas they're real pathology.

NOTE Confidence: 0.92799218

00:37:45.410 --> 00:37:47.178 So I actually like to use the terms,

NOTE Confidence: 0.92799218

00:37:47.180 --> 00:37:49.352 you know, amyloid related,

NOTE Confidence: 0.92799218

00:37:49.352 --> 00:37:51.631 you know, edema and hemosiderin.

NOTE Confidence: 0.92799218

00:37:51.631 --> 00:37:54.486 And I'll slip into those, I'm sure.

NOTE Confidence: 0.92799218

00:37:54.486 --> 00:37:57.412 But in any case, you know,

NOTE Confidence: 0.92799218

00:37:57.412 --> 00:38:00.420 Aria, there are two types.

NOTE Confidence: 0.92799218

00:38:00.420 --> 00:38:04.140 There's the RE which refused to,

NOTE Confidence: 0.92799218

00:38:04.140 --> 00:38:08.736 which refers to effusions or edema,

NOTE Confidence: 0.92799218

00:38:08.740 --> 00:38:10.750 and then there's the RH,

NOTE Confidence: 0.92799218

00:38:10.750 --> 00:38:13.642 which refers to the deposition of

NOTE Confidence: 0.92799218

00:38:13.642 --> 00:38:15.570 the blood product hemosiderin.

NOTE Confidence: 0.92799218

00:38:15.570 --> 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 --> 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 --> 00:38:35.730 why do these occur at all?

NOTE Confidence: 0.92799218

00:38:35.730 --> 00:38:38.278 It's not fully known but the leading

NOTE Confidence: 0.92799218

00:38:38.278 --> 00:38:41.090 view is that monoclonal antibodies,

NOTE Confidence: 0.92799218

00:38:41.090 --> 00:38:43.220 anti antibodies by clearing amyloid

NOTE Confidence: 0.92799218

00:38:43.220 --> 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 --> 00:38:52.168 of the blood brain barrier,

NOTE Confidence: 0.92799218

00:38:52.170 --> 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 --> 00:38:56.750 leakage of molecules that wouldn't

NOTE Confidence: 0.92799218

00:38:56.750 --> 00:38:57.774 normally pass.

NOTE Confidence: 0.92799218

00:38:57.780 --> 00:38:59.808 Drawing fluid osmotically that

NOTE Confidence: 0.92799218

00:38:59.808 --> 00:39:02.701 that's the explanation for edema and

NOTE Confidence: 0.92799218

00:39:02.701 --> 00:39:04.807 then for hemosiderin 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 --> 00:39:09.702 with with small bleeds for example.

NOTE Confidence: 0.92799218

00:39:09.710 --> 00:39:12.032 But this slide shows what these

NOTE Confidence: 0.92799218

00:39:12.032 --> 00:39:14.349 things look like on MRI scan.

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

00:39:22.489 --> 00:39:24.967 know we're looking at you know

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

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

00:39:32.746 --> 00:39:36.780 signal abnormality here in the right

00:39:36.780 --> 00:39:42.570 occipital lobe with some gyral swelling.

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

00:39:43.682 --> 00:39:48.130 we're looking at a more pure sulcal effusion,

00:39:48.130 --> 00:39:50.346 which is another way that this can present

00:39:50.346 --> 00:39:52.610 not so much parenchymal as you know,

00:39:52.610 --> 00:39:53.549 a sulcal effusion.

00:39:53.549 --> 00:39:55.740 And then in D we're looking at

00:39:55.813 --> 00:39:57.669 A at A at a very subtle case,

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 --> 00:40:04.835 gyral swelling is evident and a little

NOTE Confidence: 0.92799218

00:40:04.835 --> 00:40:06.835 bit of a circle effusion is evidence.

NOTE Confidence: 0.92799218

00:40:06.840 --> 00:40:10.064 So that would be a very subtle case

NOTE Confidence: 0.92799218

00:40:10.064 --> 00:40:12.938 with regard to Aria H as we'll see.

NOTE Confidence: 0.92799218

00:40:12.940 --> 00:40:14.980 This can come in different forms.

NOTE Confidence: 0.92799218

00:40:14.980 --> 00:40:17.506 The one shown here is microhemorrhages

NOTE Confidence: 0.92799218

00:40:17.506 --> 00:40:20.577 and that's in panel B in the red

NOTE Confidence: 0.92799218

00:40:20.577 --> 00:40:22.539 circle you see these three dots.

NOTE Confidence: 0.92799218

00:40:22.540 --> 00:40:23.880 Micro hemorrhages are defined

NOTE Confidence: 0.92799218

00:40:23.880 --> 00:40:25.555 as less than a centimeter.

NOTE Confidence: 0.92799218

00:40:25.560 --> 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 --> 00:40:32.234 So they tend to occur where edema

NOTE Confidence: 0.92799218

00:40:32.234 --> 00:40:35.198 has also occurred by the way.

NOTE Confidence: 0.92799218

00:40:35.200 --> 00:40:37.396 And we'll talk more about that.

NOTE Confidence: 0.92799218

00:40:37.400 --> 00:40:40.200 The the other forms of RH not shown

NOTE Confidence: 0.92799218

00:40:40.200 --> 00:40:43.032 here are superficial siderosis 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 --> 00:40:47.845 to find us more than a centimeter

NOTE Confidence: 0.92799218

00:40:47.845 --> 00:40:50.425 and we'll talk more about that.

NOTE Confidence: 0.92799218

00:40:50.430 --> 00:40:53.321 So now going back to the safety

NOTE Confidence: 0.92799218

00:40:53.321 --> 00:40:56.097 data for Liquin amab in light of

NOTE Confidence: 0.92799218

00:40:56.097 --> 00:40:58.900 in light of that first of all

NOTE Confidence: 0.92799218

00:40:58.900 --> 00:41:00.700 here we're looking at.

NOTE Confidence: 0.6871895

00:41:00.700 --> 00:41:05.442 The. We're looking at the the most

NOTE Confidence: 0.6871895

00:41:05.442 --> 00:41:07.360 serious adverse events that occur.

NOTE Confidence: 0.6871895

00:41:07.360 --> 00:41:10.018 So for example, you know deaths,

NOTE Confidence: 0.6871895

00:41:10.018 --> 00:41:13.560 deaths were fairly balanced 7 on placebo,

NOTE Confidence: 0.6871895

00:41:13.560 --> 00:41:15.152 6 on the Kanab.

NOTE Confidence: 0.6871895

00:41:15.152 --> 00:41:18.220 Next we look at serious adverse events,

NOTE Confidence: 0.6871895

00:41:18.220 --> 00:41:20.245 things that require for example

NOTE Confidence: 0.6871895

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

NOTE Confidence: 0.6871895

00:41:22.341 --> 00:41:24.493 want you to see here is that the,

NOTE Confidence: 0.6871895

00:41:24.500 --> 00:41:26.315 it's really only three kinds

NOTE Confidence: 0.6871895

00:41:26.315 --> 00:41:28.130 of events that are occurring

NOTE Confidence: 0.6871895

00:41:28.202 --> 00:41:30.176 more on the Kanab than placebo,

NOTE Confidence: 0.6871895

00:41:30.180 --> 00:41:32.390 it's those that are associated

NOTE Confidence: 0.6871895

00:41:32.390 --> 00:41:33.667 with these RERH.

NOTE Confidence: 0.6871895

00:41:33.667 --> 00:41:35.989 And then the third category would

NOTE Confidence: 0.6871895

00:41:35.989 --> 00:41:37.880 be infusion related reactions,

NOTE Confidence: 0.6871895

00:41:37.880 --> 00:41:41.330 you know mild hypersensitivity reactions.

NOTE Confidence: 0.6871895

00:41:41.330 --> 00:41:44.108 All other SME's are actually you

NOTE Confidence: 0.6871895

00:41:44.108 --> 00:41:46.770 know quite balanced between drug and

NOTE Confidence: 0.6871895

00:41:46.770 --> 00:41:49.311 placebo and and again as much as

NOTE Confidence: 0.6871895

00:41:49.311 --> 00:41:52.148 these essays are more common on drug,

NOTE Confidence: 0.6871895

00:41:52.150 --> 00:41:54.046 they're they're still not very common.

NOTE Confidence: 0.6871895

00:41:54.050 --> 00:41:55.807 I mean they're all in the order

NOTE Confidence: 0.6871895

00:41:55.807 --> 00:41:56.970 of 1% frequency.

NOTE Confidence: 0.877360036

00:41:59.460 --> 00:42:03.023 This slide shows you know common adverse

NOTE Confidence: 0.877360036

00:42:03.023 --> 00:42:05.939 events now including non serious adverse

NOTE Confidence: 0.877360036

00:42:05.939 --> 00:42:09.462 events and and again I think the the

NOTE Confidence: 0.877360036

00:42:09.462 --> 00:42:12.662 real take home message is that it's the

NOTE Confidence: 0.877360036

00:42:12.662 --> 00:42:15.440 it's the ones in these three categories

NOTE Confidence: 0.877360036

00:42:15.440 --> 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 --> 00:42:23.034 related reactions RER AH everything

NOTE Confidence: 0.877360036

00:42:23.034 --> 00:42:26.092 else down at the bottom of the slide is

NOTE Confidence: 0.877360036

00:42:26.092 --> 00:42:28.570 is not is really not more common on Lebanon.

NOTE Confidence: 0.877360036

00:42:28.570 --> 00:42:30.826 So want to just take a moment to

NOTE Confidence: 0.877360036

00:42:30.826 --> 00:42:32.821 focus on infusion related reactions

NOTE Confidence: 0.877360036

00:42:32.821 --> 00:42:35.999 because I won't talk about these again.

NOTE Confidence: 0.877360036

00:42:36.000 --> 00:42:40.292 So 26.4% with like Kanab,

NOTE Confidence: 0.877360036

00:42:40.292 --> 00:42:42.272 7.4% with placebo.

NOTE Confidence: 0.877360036

00:42:42.272 --> 00:42:45.732 These tend to be almost always

NOTE Confidence: 0.877360036

00:42:45.732 --> 00:42:47.160 mild to moderate,

NOTE Confidence: 0.877360036

00:42:47.160 --> 00:42:49.383 you know 96% of them are they tend to

NOTE Confidence: 0.877360036

00:42:49.383 --> 00:42:51.357 occur with the very first infusion,

NOTE Confidence: 0.877360036

00:42:51.360 --> 00:42:53.370 most commonly the only occur once.

NOTE Confidence: 0.7749822

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

NOTE Confidence: 0.7749822

00:42:59.070 --> 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 --> 00:43:07.532 us think this is really the most

NOTE Confidence: 0.7749822

00:43:07.532 --> 00:43:09.777 important toxicity of 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 --> 00:43:18.170 and necessitates you know pausing

NOTE Confidence: 0.7749822

00:43:18.257 --> 00:43:22.410 infusions until it resolves. Um.

NOTE Confidence: 0.7749822

00:43:22.410 --> 00:43:26.146 So the the key statistic here that you

NOTE Confidence: 0.7749822

00:43:26.146 --> 00:43:30.038 can see is 12.6% frequency on LEINAD,

NOTE Confidence: 0.7749822

00:43:30.038 --> 00:43:31.270 1.7 on placebo.

NOTE Confidence: 0.7749822

00:43:31.270 --> 00:43:33.550 You know why does it occur on placebo?

NOTE Confidence: 0.7749822

00:43:33.550 --> 00:43:36.502 Well it it does occur spontaneously

NOTE Confidence: 0.7749822

00:43:36.502 --> 00:43:39.510 in related to amyloid angiopathy.

NOTE Confidence: 0.7749822

00:43:39.510 --> 00:43:42.147 You know CIA people with a lot of of

NOTE Confidence: 0.7749822

00:43:42.147 --> 00:43:43.710 amyloid angiopathy are disqualified

NOTE Confidence: 0.7749822

00:43:43.710 --> 00:43:46.510 from the study in the 1st place.

NOTE Confidence: 0.7749822

00:43:46.510 --> 00:43:48.463 You know if they have more than

NOTE Confidence: 0.7749822

00:43:48.463 --> 00:43:49.599 four microhemorrhages at the

NOTE Confidence: 0.7749822

00:43:49.599 --> 00:43:51.063 start they they don't enroll in

NOTE Confidence: 0.7749822

00:43:51.063 --> 00:43:52.599 the study for safety reasons.

NOTE Confidence: 0.7749822

00:43:52.600 --> 00:43:55.328 But there can be spontaneous cases of this.

NOTE Confidence: 0.832082954

00:43:57.360 --> 00:44:01.418 And. Symptomatic cases are only 2.8%,

NOTE Confidence: 0.832082954

00:44:01.418 --> 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 --> 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 --> 00:44:10.170 confusion, things like that.

NOTE Confidence: 0.832082954

00:44:10.170 --> 00:44:12.960 And and you know and in general

NOTE Confidence: 0.832082954

00:44:12.960 --> 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 --> 00:44:19.250 I view these as very manageable numbers.

NOTE Confidence: 0.832082954

00:44:19.250 --> 00:44:21.077 I mean I will tell you that

NOTE Confidence: 0.832082954

00:44:21.077 --> 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 --> 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 --> 00:44:34.180 these are substantially lower

NOTE Confidence: 0.832082954

00:44:34.180 --> 00:44:36.820 numbers than the other trials report.

NOTE Confidence: 0.721029231153846

00:44:41.850 --> 00:44:44.762 Now a little more detail on Aria H

NOTE Confidence: 0.721029231153846

00:44:44.762 --> 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 --> 00:44:54.430 a blood product that shows up on the.

NOTE Confidence: 0.798711484545454

00:44:54.430 --> 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 --> 00:45:02.510 Ah, you know is generally

NOTE Confidence: 0.798711484545454

00:45:02.510 --> 00:45:04.110 comes in three categories,

NOTE Confidence: 0.798711484545454

00:45:04.110 --> 00:45:05.154 microhemorrhages that we

NOTE Confidence: 0.798711484545454

00:45:05.154 --> 00:45:07.242 saw on the on the image,

NOTE Confidence: 0.798711484545454

00:45:07.250 --> 00:45:09.780 they're less than a centimeter.

NOTE Confidence: 0.798711484545454

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

NOTE Confidence: 0.798711484545454

00:45:13.224 --> 00:45:17.165 a thin deposition of hemosiderin on the

NOTE Confidence: 0.798711484545454

00:45:17.165 --> 00:45:21.650 brain surface actually in the sub peel space.

NOTE Confidence: 0.798711484545454

00:45:21.650 --> 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 --> 00:45:30.030 Well it's more than a centimeter you know

NOTE Confidence: 0.798711484545454

00:45:30.030 --> 00:45:32.709 it's it's the delineation between the two.

NOTE Confidence: 0.798711484545454

00:45:32.710 --> 00:45:35.294 So what you can see overall here is

NOTE Confidence: 0.798711484545454

00:45:35.294 --> 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 --> 00:45:47.940 Of real note though is that the increase

NOTE Confidence: 0.798711484545454

00:45:48.048 --> 00:45:51.976 in like cannab is really area and the.

NOTE Confidence: 0.798711484545454

00:45:51.976 --> 00:45:53.824 Actually micro hemorrhages that

NOTE Confidence: 0.798711484545454

00:45:53.824 --> 00:45:55.710 are associated with edema.

NOTE Confidence: 0.798711484545454

00:45:55.710 --> 00:45:59.166 So if you take cases where there's no edema,

NOTE Confidence: 0.798711484545454

00:45:59.170 --> 00:46:01.135 these actually aren't more common

NOTE Confidence: 0.798711484545454

00:46:01.135 --> 00:46:02.707 on drug than placebo.

NOTE Confidence: 0.798711484545454

00:46:02.710 --> 00:46:05.302 And again they have for a lot of

NOTE Confidence: 0.798711484545454

00:46:05.302 --> 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 --> 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 --> 00:46:26.196 and it also is some, you know,

NOTE Confidence: 0.647796774

00:46:26.196 --> 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 --> 00:46:37.395 which have caught a lot of press,

NOTE Confidence: 0.647796774

00:46:37.395 --> 00:46:39.300 especially, you know,

NOTE Confidence: 0.647796774

00:46:39.300 --> 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 --> 00:46:46.190 as important as they are,

NOTE Confidence: 0.647796774

00:46:46.190 --> 00:46:49.130 I think they've gotten a real inordinate

NOTE Confidence: 0.647796774

00:46:49.130 --> 00:46:52.000 and very imbalanced coverage in the press.

NOTE Confidence: 0.647796774

00:46:52.000 --> 00:46:55.516 So, so just to be clear.

NOTE Confidence: 0.647796774

00:46:55.520 --> 00:46:58.044 In the double-blind study,

NOTE Confidence: 0.647796774

00:46:58.044 --> 00:47:01.287 there was one fatal lobar hemorrhage,

NOTE Confidence: 0.647796774

00:47:01.287 --> 00:47:04.430 and it occurred in the placebo group.

NOTE Confidence: 0.647796774

00:47:04.430 --> 00:47:06.878 The two that have been reported in the

NOTE Confidence: 0.647796774

00:47:06.878 --> 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 --> 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 --> 00:47:20.537 left MCA stroke occlusion and was

NOTE Confidence: 0.647796774

00:47:20.537 --> 00:47:24.630 administered TPA emergently in the ER.

NOTE Confidence: 0.647796774

00:47:24.630 --> 00:47:27.073 And those of you familiar know that

NOTE Confidence: 0.647796774

00:47:27.073 --> 00:47:29.300 there's a there's a substantial risk

NOTE Confidence: 0.647796774

00:47:29.300 --> 00:47:31.883 of major hemorrhage with with TPA and

NOTE Confidence: 0.647796774

00:47:31.953 --> 00:47:34.459 that's what happened and and she died.

NOTE Confidence: 0.647796774

00:47:34.460 --> 00:47:37.612 The second case is of a A a

NOTE Confidence: 0.647796774

00:47:37.612 --> 00:47:40.078 fairly frail 87 year old man.

NOTE Confidence: 0.647796774

00:47:40.080 --> 00:47:41.070 He's actually older than would

NOTE Confidence: 0.647796774

00:47:41.070 --> 00:47:42.320 have been allowed in the study.

NOTE Confidence: 0.647796774

00:47:42.320 --> 00:47:45.006 At the start of the study E4 non

NOTE Confidence: 0.647796774

00:47:45.006 --> 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 --> 00:47:52.108 he had a lobar hemorrhage and and

NOTE Confidence: 0.647796774

00:47:52.108 --> 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 --> 00:47:56.509 atrial fibrillation,

NOTE Confidence: 0.647796774

00:47:56.510 --> 00:47:58.946 he had an MRI and which is

NOTE Confidence: 0.647796774

00:47:58.946 --> 00:48:00.879 probably what he died from.

NOTE Confidence: 0.647796774

00:48:00.880 --> 00:48:02.014 So you know,

NOTE Confidence: 0.647796774

00:48:02.014 --> 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 --> 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 --> 00:48:13.454 I would have said that the case on

NOTE Confidence: 0.647796774

00:48:13.454 --> 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 --> 00:48:21.752 And if you look at the overall

NOTE Confidence: 0.647796774

00:48:21.752 --> 00:48:24.051 frequency of these cases, it's,

NOTE Confidence: 0.647796774

00:48:24.051 --> 00:48:26.178 it's about one in 1000, right,

NOTE Confidence: 0.647796774

00:48:26.178 --> 00:48:29.286 it's 0.1% for people taking placebo.

NOTE Confidence: 0.647796774

00:48:29.290 --> 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 --> 00:48:35.766 the greater exposure to lucama.

NOTE Confidence: 0.647796774

00:48:35.770 --> 00:48:38.040 On the open label extension.

NOTE Confidence: 0.647796774

00:48:38.040 --> 00:48:39.496 So I think we need to balance

NOTE Confidence: 0.647796774

00:48:39.496 --> 00:48:41.101 you know what we hear in the

NOTE Confidence: 0.647796774

00:48:41.101 --> 00:48:42.493 press with some of these numbers.

NOTE Confidence: 0.647796774

00:48:42.500 --> 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 --> 00:48:50.640 can be catastrophic events like this,

NOTE Confidence: 0.647796774

00:48:50.640 --> 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 --> 00:48:59.578 and uniformly fatal.

NOTE Confidence: 0.647796774

00:48:59.580 --> 00:49:01.788 And in fact when we talk to patients

NOTE Confidence: 0.647796774

00:49:01.788 --> 00:49:03.480 and their families about these

NOTE Confidence: 0.647796774

00:49:03.480 --> 00:49:05.640 risks in relation to these drugs,

NOTE Confidence: 0.647796774

00:49:05.640 --> 00:49:06.930 people who are interested in

NOTE Confidence: 0.647796774

00:49:06.930 --> 00:49:08.220 these drugs to begin with.

NOTE Confidence: 0.647796774

00:49:08.220 --> 00:49:10.068 Which are the people I talked to?

NOTE Confidence: 0.647796774

00:49:10.070 --> 00:49:12.650 It's you really don't hear

NOTE Confidence: 0.647796774

00:49:12.650 --> 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 --> 00:49:23.107 Now I want to finish with biomarkers

NOTE Confidence: 0.647796774

00:49:23.110 --> 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 --> 00:49:28.821 bit as interesting as the as

NOTE Confidence: 0.647796774

00:49:28.821 --> 00:49:30.536 the you know clinical effects.

NOTE Confidence: 0.647796774

00:49:30.536 --> 00:49:33.840 By way of background when we talk about

NOTE Confidence: 0.647796774

00:49:33.913 --> 00:49:36.449 biomarkers and Alzheimer's disease,

NOTE Confidence: 0.647796774

00:49:36.450 --> 00:49:38.916 I want to introduce the the

NOTE Confidence: 0.647796774

00:49:38.916 --> 00:49:41.450 current notion of of of Alzheimer's

NOTE Confidence: 0.647796774

00:49:41.450 --> 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 --> 00:49:50.666 T for tile and for neurodegeneration.

NOTE Confidence: 0.591725844285714

00:49:50.670 --> 00:49:53.316 So most people with Alzheimer's disease,

76

00:49:53.320 --> 00:49:55.532 you know, start out in the yellow

00:49:55.532 --> 00:49:57.600 circle that is amyloid doesn't.

00:49:57.600 --> 00:50:00.316 And what that means is the amyloid

00:50:00.316 --> 00:50:02.800 pathogenesis tends to be detected first.

00:50:02.800 --> 00:50:06.100 From there, if they have Alzheimer's,

00:50:06.100 --> 00:50:07.564 eventually Tau pathology

00:50:07.564 --> 00:50:09.516 will also be detectable.

00:50:09.520 --> 00:50:10.860 It may be there earlier,

00:50:10.860 --> 00:50:12.420 but the ways it's detected,

00:50:12.420 --> 00:50:14.340 you know, tend to to follow.

00:50:14.340 --> 00:50:17.034 And important thing is that Alzheimer's

00:50:17.034 --> 00:50:21.162 just defined by this intersection, A plus.

00:50:21.162 --> 00:50:24.367 Key is equals Alzheimer's disease.

00:50:24.370 --> 00:50:27.298 These people also will will progress

00:50:27.298 --> 00:50:29.726 to have neurodegeneration the blue

00:50:29.726 --> 00:50:32.120 circle and then there's the green

NOTE Confidence: 0.591725844285714

00:50:32.120 --> 00:50:34.950 circle which is cognitive impairment.

NOTE Confidence: 0.591725844285714

00:50:34.950 --> 00:50:37.337 And important to point out that people

NOTE Confidence: 0.591725844285714

00:50:37.337 --> 00:50:40.692 kind of can have all of these pathologies

NOTE Confidence: 0.591725844285714

00:50:40.692 --> 00:50:42.947 and still remain cognitively normal.

NOTE Confidence: 0.591725844285714

00:50:42.950 --> 00:50:45.421 And it's the people are cognitively normal

NOTE Confidence: 0.591725844285714

00:50:45.421 --> 00:50:47.990 who may may represent the best target

NOTE Confidence: 0.591725844285714

00:50:47.990 --> 00:50:50.740 for treatment as well sake at the end.

NOTE Confidence: 0.591725844285714

00:50:50.740 --> 00:50:54.100 So what does lecanu mob do for amyloid?

NOTE Confidence: 0.591725844285714

00:50:54.100 --> 00:50:55.156 First of all?

NOTE Confidence: 0.591725844285714

00:50:55.156 --> 00:50:58.720 Well, we saw what it did for amyloid pet.

NOTE Confidence: 0.591725844285714

00:50:58.720 --> 00:51:00.540 What about soluble amyloid,

NOTE Confidence: 0.591725844285714

00:51:00.540 --> 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 --> 00:51:08.500 And that's what's shown here.

NOTE Confidence: 0.591725844285714

00:51:08.500 --> 00:51:09.814 On the left,

NOTE Confidence: 0.591725844285714

00:51:09.814 --> 00:51:12.880 we're looking at lacanada effects on CSF,

NOTE Confidence: 0.591725844285714

00:51:12.880 --> 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 --> 00:51:18.183 the malignant one.

NOTE Confidence: 0.591725844285714

00:51:18.183 --> 00:51:19.507 In the upper right,

NOTE Confidence: 0.591725844285714

00:51:19.510 --> 00:51:22.561 we're looking at the ratio of 42 to 40

NOTE Confidence: 0.591725844285714

00:51:22.561 --> 00:51:26.329 and in the lower right we're looking at

NOTE Confidence: 0.591725844285714

00:51:26.329 --> 00:51:29.138 the corresponding ratio in blood plasma.

NOTE Confidence: 0.591725844285714

00:51:29.140 --> 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 --> 00:51:35.730 actually these all go down,

NOTE Confidence: 0.591725844285714

00:51:35.730 --> 00:51:36.999 not up because,

NOTE Confidence: 0.591725844285714

00:51:36.999 --> 00:51:39.960 and that's thought to occur because they're

NOTE Confidence: 0.591725844285714

00:51:40.034 --> 00:51:43.184 being aggregated and deposited in the brain,

NOTE Confidence: 0.591725844285714

00:51:43.190 --> 00:51:44.950 you know, as plaques.

NOTE Confidence: 0.591725844285714

00:51:44.950 --> 00:51:47.262 So up is good, you know,

NOTE Confidence: 0.591725844285714

00:51:47.262 --> 00:51:48.090 in these cases.

NOTE Confidence: 0.591725844285714

00:51:48.090 --> 00:51:50.322 And what you can see is that although

NOTE Confidence: 0.591725844285714

00:51:50.322 --> 00:51:52.810 there's no effective lukianov on EBITDA 40,

NOTE Confidence: 0.591725844285714

00:51:52.810 --> 00:51:56.202 the more important a beta 42, you know,

NOTE Confidence: 0.591725844285714

00:51:56.202 --> 00:51:59.460 there's a definite normalizing of the A beta.

NOTE Confidence: 0.591725844285714

00:51:59.460 --> 00:52:01.264 Aggregation process and that's

NOTE Confidence: 0.591725844285714

00:52:01.264 --> 00:52:04.376 also shown in the ratio of abeta

NOTE Confidence: 0.591725844285714

00:52:04.376 --> 00:52:06.644 42 to 40 and it's even shown

NOTE Confidence: 0.591725844285714

00:52:06.644 --> 00:52:09.037 in the same ratio in plasma.

NOTE Confidence: 0.752258933333333

00:52:11.320 --> 00:52:13.870 What about Tau?

NOTE Confidence: 0.752258933333333

00:52:13.870 --> 00:52:17.958 Well, with Tau there are 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 --> 00:52:21.478 there's the phosphorylation of

NOTE Confidence: 0.752258933333333

00:52:21.478 --> 00:52:24.739 soluble Tau which is thought to be

NOTE Confidence: 0.752258933333333

00:52:24.739 --> 00:52:27.229 an early marker of Tau pathogenesis,

NOTE Confidence: 0.752258933333333

00:52:27.230 --> 00:52:29.410 and that's what's shown here.

NOTE Confidence: 0.752258933333333

00:52:29.410 --> 00:52:32.380 What we can see is that for phospho

NOTE Confidence: 0.752258933333333

00:52:32.380 --> 00:52:35.800 Tau 181 steady increases in people

NOTE Confidence: 0.752258933333333

00:52:35.800 --> 00:52:38.794 on placebo and decreases relative

NOTE Confidence: 0.752258933333333

00:52:38.794 --> 00:52:42.334 to that and people taking liking

NOTE Confidence: 0.752258933333333

00:52:42.334 --> 00:52:45.619 amab in both CSF and plasma.

NOTE Confidence: 0.81702165

00:52:48.480 --> 00:52:52.647 Tao pet on the other hand is measuring the.

NOTE Confidence: 0.81702165

00:52:52.650 --> 00:52:55.200 The is looking at the aggregation

NOTE Confidence: 0.81702165

00:52:55.200 --> 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 --> 00:53:04.961 tangles or dystrophic neurites in

NOTE Confidence: 0.81702165

00:53:04.961 --> 00:53:08.066 brain can be measured on a PET scan.

NOTE Confidence: 0.81702165

00:53:08.070 --> 00:53:10.653 In this case we're looking at pet

NOTE Confidence: 0.81702165

00:53:10.653 --> 00:53:12.829 data from multiple brain regions.

NOTE Confidence: 0.81702165

00:53:12.830 --> 00:53:14.720 Although I should point out that the

NOTE Confidence: 0.81702165

00:53:14.720 --> 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 --> 00:53:20.926 are represent earlier Brock stages.

NOTE Confidence: 0.81702165

00:53:20.930 --> 00:53:25.763 And what we can see here is that for

NOTE Confidence: 0.81702165

00:53:25.770 --> 00:53:27.850 three different temporal lobe regions

NOTE Confidence: 0.81702165

00:53:27.850 --> 00:53:29.930 and medial temporal lobe so-called.

NOTE Confidence: 0.81702165

00:53:29.930 --> 00:53:32.678 Meta temporal and a whole temporal.

NOTE Confidence: 0.81702165

00:53:32.680 --> 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 --> 00:53:39.400 blunting bilican amab compared

NOTE Confidence: 0.81702165

00:53:39.400 --> 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 --> 00:53:45.210 Tau deposition on PET scan.

NOTE Confidence: 0.737305082666667

00:53:49.000 --> 00:53:51.946 One measure of end of neurodegeneration

NOTE Confidence: 0.737305082666667

00:53:51.946 --> 00:53:54.424 would be volumetric MRI and

NOTE Confidence: 0.737305082666667

00:53:54.424 --> 00:53:56.168 that's shown shown here.

NOTE Confidence: 0.737305082666667

00:53:56.170 --> 00:53:58.025 First of all in the top row

NOTE Confidence: 0.737305082666667

00:53:58.025 --> 00:53:59.848 we're looking at the effects of

NOTE Confidence: 0.737305082666667

00:53:59.848 --> 00:54:01.774 lecan amab on whole brain volume,

NOTE Confidence: 0.737305082666667

00:54:01.780 --> 00:54:03.448 cortical thickness and

NOTE Confidence: 0.737305082666667

00:54:03.448 --> 00:54:05.116 lateral ventricular volume.

NOTE Confidence: 0.737305082666667

00:54:05.120 --> 00:54:07.740 And maybe paradoxically Kanab is

NOTE Confidence: 0.737305082666667

00:54:07.740 --> 00:54:09.836 associated with greater atrophy

NOTE Confidence: 0.737305082666667

00:54:09.836 --> 00:54:12.139 and all of these measures.

NOTE Confidence: 0.737305082666667

00:54:12.140 --> 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 --> 00:54:17.243 with anti amyloid therapies and

NOTE Confidence: 0.737305082666667

00:54:17.243 --> 00:54:18.599 and one simple explanation.

NOTE Confidence: 0.737305082666667

00:54:18.600 --> 00:54:21.864 Maybe simply that it represents plaque

NOTE Confidence: 0.737305082666667

00:54:21.864 --> 00:54:24.690 clearance which which reduces volume.

NOTE Confidence: 0.737305082666667

00:54:24.690 --> 00:54:26.860 The bottom row shows hippocampal

NOTE Confidence: 0.737305082666667

00:54:26.860 --> 00:54:29.872 volumes and in this case that effect

NOTE Confidence: 0.737305082666667

00:54:29.872 --> 00:54:33.240 is not seen and in fact like Kanab

NOTE Confidence: 0.737305082666667

00:54:33.336 --> 00:54:36.684 is associated with less atrophy in

NOTE Confidence: 0.737305082666667

00:54:36.684 --> 00:54:39.840 hippocampal volumes at end of study.

NOTE Confidence: 0.737305082666667

00:54:39.840 --> 00:54:43.648 So where do we go next from here?

NOTE Confidence: 0.737305082666667

00:54:43.650 --> 00:54:46.251 You know we can't amab may be ready for

NOTE Confidence: 0.737305082666667

00:54:46.251 --> 00:54:48.256 the clinic you know remains remains

NOTE Confidence: 0.737305082666667

00:54:48.256 --> 00:54:51.387 to be seen by you know FDA and and CMS.

NOTE Confidence: 0.737305082666667

00:54:51.390 --> 00:54:54.462 It did receive the accelerated approval

NOTE Confidence: 0.737305082666667

00:54:54.462 --> 00:54:57.540 based on plaque clearance January 6th.

NOTE Confidence: 0.737305082666667

00:54:57.540 --> 00:54:58.970 Umm, and it was submitted.

NOTE Confidence: 0.737305082666667

00:54:58.970 --> 00:55:01.538 They submitted for traditional approval on

NOTE Confidence: 0.737305082666667

00:55:01.538 --> 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 --> 00:55:06.660 probably late spring.

NOTE Confidence: 0.737305082666667

00:55:06.660 --> 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 --> 00:55:13.304 I just want to highlight here in the

NOTE Confidence: 0.737305082666667

00:55:13.304 --> 00:55:15.637 middle though that this whole issue

NOTE Confidence: 0.737305082666667

00:55:15.637 --> 00:55:17.672 of accelerated approval based on

NOTE Confidence: 0.737305082666667

00:55:17.672 --> 00:55:19.678 biomarker is really controversial.

NOTE Confidence: 0.737305082666667

00:55:19.680 --> 00:55:21.240 And for anyone interested,

NOTE Confidence: 0.737305082666667

00:55:21.240 --> 00:55:23.580 we're going to have a webinar

NOTE Confidence: 0.737305082666667

00:55:23.655 --> 00:55:25.119 debate next Thursday.

NOTE Confidence: 0.737305082666667

00:55:25.120 --> 00:55:26.480 Dennis Selkoe's going to

NOTE Confidence: 0.737305082666667

00:55:26.480 --> 00:55:27.500 take the affirmative.

NOTE Confidence: 0.737305082666667

00:55:27.500 --> 00:55:28.970 That this is a ready,

NOTE Confidence: 0.737305082666667

00:55:28.970 --> 00:55:29.994 we're ready for this,

NOTE Confidence: 0.737305082666667

00:55:29.994 --> 00:55:32.090 so I'm going to take the negative.

NOTE Confidence: 0.737305082666667

00:55:32.090 --> 00:55:32.876 Here's the link.

NOTE Confidence: 0.737305082666667

00:55:32.876 --> 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 --> 00:55:39.187 can just e-mail me and I'll make

NOTE Confidence: 0.737305082666667

00:55:39.187 --> 00:55:40.782 sure that you get registered.

NOTE Confidence: 0.737305082666667

00:55:40.790 --> 00:55:43.135 The other where to next is is

NOTE Confidence: 0.737305082666667

00:55:43.135 --> 00:55:45.450 where we go scientifically.

NOTE Confidence: 0.737305082666667

00:55:45.450 --> 00:55:48.106 And I think these results really beg the

NOTE Confidence: 0.737305082666667

00:55:48.106 --> 00:55:50.109 question about earlier intervention,

NOTE Confidence: 0.737305082666667

00:55:50.110 --> 00:55:52.384 you know then clarity AD which

NOTE Confidence: 0.737305082666667

00:55:52.384 --> 00:55:54.530 was in early symptomatic disease,

NOTE Confidence: 0.737305082666667

00:55:54.530 --> 00:55:56.986 I think we need to go to pre

NOTE Confidence: 0.737305082666667

00:55:56.986 --> 00:55:58.595 symptomatic disease which is what

NOTE Confidence: 0.737305082666667

00:55:58.595 --> 00:56:00.702 the ahead study does and this

NOTE Confidence: 0.737305082666667

00:56:00.702 --> 00:56:02.857 study was started already about

NOTE Confidence: 0.737305082666667

00:56:02.857 --> 00:56:04.520 almost three years ago.

NOTE Confidence: 0.737305082666667

00:56:04.520 --> 00:56:06.920 And we fortunately chose the cannabis

NOTE Confidence: 0.737305082666667

00:56:06.920 --> 00:56:09.959 the drug before we knew these results.

NOTE Confidence: 0.737305082666667

00:56:09.960 --> 00:56:12.606 But there are two parts of.

NOTE Confidence: 0.737305082666667

00:56:12.610 --> 00:56:14.830 The head study people in the

NOTE Confidence: 0.737305082666667

00:56:14.830 --> 00:56:17.475 so-called a 4-5 arm have elevated

NOTE Confidence: 0.737305082666667

00:56:17.475 --> 00:56:20.175 and clearly elevated brain amyloid.

NOTE Confidence: 0.737305082666667

00:56:20.180 --> 00:56:23.270 In the A3 portion they have

NOTE Confidence: 0.737305082666667

00:56:23.270 --> 00:56:24.815 sub threshold elevation,

NOTE Confidence: 0.737305082666667

00:56:24.820 --> 00:56:26.794 you don't it's it looks visually normal

NOTE Confidence: 0.737305082666667

00:56:26.794 --> 00:56:29.144 but we know these folks are destined

NOTE Confidence: 0.737305082666667

00:56:29.144 --> 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 --> 00:56:35.334 of of intervention.

NOTE Confidence: 0.737305082666667

00:56:35.340 --> 00:56:38.088 Your head study design is shown

NOTE Confidence: 0.737305082666667

00:56:38.088 --> 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 --> 00:56:46.808 arm with clearly elevated amyloid.

NOTE Confidence: 0.737305082666667

00:56:46.810 --> 00:56:49.127 Start out every two week infusions for

NOTE Confidence: 0.737305082666667

00:56:49.127 --> 00:56:51.968 two years and then go to every four weeks.

NOTE Confidence: 0.737305082666667

00:56:51.970 --> 00:56:53.282 Those with the intermediate

NOTE Confidence: 0.737305082666667

00:56:53.282 --> 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: 0.737305082666667

00:56:57.410 --> 00:57:00.450 Maybe a three study.

NOTE Confidence: 0.737305082666667

00:57:00.450 --> 00:57:04.050 So in summary of what I've shown you,

NOTE Confidence: 0.737305082666667

00:57:04.050 --> 00:57:06.708 the cannab treatment met all primary

NOTE Confidence: 0.737305082666667

00:57:06.708 --> 00:57:08.480 and secondary endpoints versus

NOTE Confidence: 0.737305082666667

00:57:08.548 --> 00:57:11.242 placebo at 18 months with highly

NOTE Confidence: 0.737305082666667

00:57:11.242 --> 00:57:13.038 significant differences starting at

NOTE Confidence: 0.833930258636364

00:57:13.112 --> 00:57:15.270 six months. And I think one of

NOTE Confidence: 0.833930258636364

00:57:15.270 --> 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 --> 00:57:21.479 broad range of endpoints and subgroups.

NOTE Confidence: 0.833930258636364

00:57:21.480 --> 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 --> 00:57:31.820 published studies with other antibodies.

NOTE Confidence: 0.833930258636364

00:57:31.820 --> 00:57:34.268 Biomarker studies revealed that we cannot

NOTE Confidence: 0.833930258636364

00:57:34.268 --> 00:57:37.024 have improved both of the essential

NOTE Confidence: 0.833930258636364

00:57:37.024 --> 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 --> 00:57:45.248 CSF and blood plasma.

NOTE Confidence: 0.833930258636364

00:57:45.248 --> 00:57:48.116 And this indicates biological

NOTE Confidence: 0.833930258636364

00:57:48.116 --> 00:57:49.550 disease modification.

NOTE Confidence: 0.833930258636364

00:57:49.550 --> 00:57:51.370 The brain MRI volumetric analysis

NOTE Confidence: 0.833930258636364

00:57:51.370 --> 00:57:53.747 indicated that like Canada was associated

NOTE Confidence: 0.833930258636364

00:57:53.747 --> 00:57:55.747 with reduced hippocampal atrophy,

NOTE Confidence: 0.833930258636364

00:57:55.750 --> 00:57:59.122 but greater global and cortical atrophy

NOTE Confidence: 0.833930258636364

00:57:59.122 --> 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 --> 00:58:07.817 with the decision on full approval

NOTE Confidence: 0.833930258636364

00:58:07.817 --> 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 --> 00:58:14.034 Medicare will revise coverage

NOTE Confidence: 0.833930258636364

00:58:14.034 --> 00:58:15.823 decision and last you.

NOTE Confidence: 0.833930258636364

00:58:15.823 --> 00:58:18.700 Had to study is investigating were earlier.

NOTE Confidence: 0.833930258636364

00:58:18.700 --> 00:58:21.020 Whether early or pre,

NOTE Confidence: 0.833930258636364

00:58:21.020 --> 00:58:23.340 symptomatic intervention may be

NOTE Confidence: 0.833930258636364

00:58:23.340 --> 00:58:26.349 associated with greater effect sizes.

NOTE Confidence: 0.833930258636364

00:58:26.350 --> 00:58:29.078 So I I thank you for your attention

NOTE Confidence: 0.833930258636364

00:58:29.078 --> 00:58:30.999 and I'll take questions.