We're good. OK, OK, great.

There are times a charm.

So uhm so uh thanks it’s been great to hear some of the talks from the morning I.

I think one of the things I was going to say and I’ll, make mine a little bit more informal.

So really, if people want to ask

questions even in between,

that’ll be fine.

One of the things that we did in

inviting our trial pies was make a

request today that they simply didn’t
talk about the protocol and the design.

One. I think a lot of us have.

Heard that that you know might

be a little bit, you know,

but what we thought we could do

and I think this is an originally

Lauren Sansing’s idea to you know,

to ask him a little bit about

These aren’t the things you would

These aren’t the things you would

find in the protocol or the lead

up that that might be relevant when
00:00:56.350 --> 00:00:57.928 you’re thinking about your own trial,
NOTE Confidence: 0.870504936
00:00:57.930 --> 00:00:59.268 because all of these things they
NOTE Confidence: 0.870504936
00:00:59.268 --> 00:01:00.709 always do have a back story.
NOTE Confidence: 0.870504936
00:01:00.710 --> 00:01:01.904 Every little detail,
NOTE Confidence: 0.870504936
00:01:01.904 --> 00:01:04.292 and the first thing really is,
NOTE Confidence: 0.870504936
00:01:04.300 --> 00:01:05.164 you know the waste.
NOTE Confidence: 0.870504936
00:01:05.164 --> 00:01:06.754 One of the things that I think
NOTE Confidence: 0.870504936
00:01:06.754 --> 00:01:08.224 about at the beginning of really
NOTE Confidence: 0.870504936
00:01:08.224 --> 00:01:10.033 most of the projects I started is
NOTE Confidence: 0.870504936
00:01:10.033 --> 00:01:11.652 just don’t say the choice of team
NOTE Confidence: 0.870504936
00:01:11.652 --> 00:01:13.344 but just the team that you either
NOTE Confidence: 0.870504936
00:01:13.344 --> 00:01:15.038 choose or that you end up working
NOTE Confidence: 0.870504936
00:01:15.094 --> 00:01:16.578 with and a little bit of both.
NOTE Confidence: 0.870504936
00:01:16.580 --> 00:01:19.364 And you know I want to just mention
NOTE Confidence: 0.870504936
00:01:19.364 --> 00:01:21.456 a couple of people, of course.
NOTE Confidence: 0.870504936
There are a lot of folks that are involved in a clinical trial, but you know, one of the things that I would say I think is as many of you know, I'm a critical care neurologist and you know, here I was trying to think about proposing a stroke prevention trial, so I thought that you know people might laugh and find that a little bit funny. Doing stroke prevention is something that I always wanted to do ever since fellowship and it just happened to be that my clinical interests were mostly in sort of acute neurology. So a few years ago I before aspire,
you know where it’s nice at Yale.

We have sabbaticals every so often and so I had a sabbatical and I used that experience to really think about how to design and think about doing a prevention trial in a disease that I did know something about and was sort of passionate about and there was no interest.

And in doing that one of the first things that I did was reach out to a colleague who was many of you know who, Monica Mellow.
As my copii at Cornell, and I say this with great respect to everyone on the call. But you know, one of the reasons we reached out and I started working with him was one because of his, you know, deep and recent experience in getting Arcadia off the ground. Even though it was hemorrhaging ischemic strokes. Some of the questions and practical interventions were going to be very much the same, and also because I really thought from our generation he was really one of the nicest,
The smartest people in the field and so being able to capture. Both of those things you know was a great opportunity. The other thing that ended up playing a big role for me. We’ve had a lot of folks in our steering committee, but just being here at Yale was being close to Walt Kernan. And as all of you know, I mean, I think many of you, Karen and others were involved in the IRIS trial, which was really only one of the
one of the few sort of successful prevention trials in NIH history, at least by efficacy outcome, and you know, to have that experience was very helpful. To have in hand and thinking about the concept but even big picture questions, I remember one of the things that Walt asked me at the beginning was, do you really want to commit potentially 7 to 10 years of your life? You know, before you embark on an endeavor like that, you gotta really think about that. So that was very helpful. The 4th person I haven’t put here and
that’s because she’s oftentimes pretty humble about these kinds of things.

And it is, you know, if you go to Google pictures, you really cannot even find a picture of her. Really quite remarkable, So Catherine Viscol is some of the pictures she did send me of herself, which in some ways you know it’s it’s not not an inappropriate picture.
this Coley is is not a clinician, but actually has been involved in stroke investigation. You know, for many many years and I I don’t know if people at Yale even know this. Sort of having some of these slides out of order, what’s up? But you know Catherine. Actually, you know has a CV in some ways that you know some stroke investigators would never have, even at the course of their whole career. And you know she happened to have this rich experience in thinking about not just conducting the trial,
but analyzing it, reporting it
really doing everything from A-Z.
Not only in these studies that you see here,
but all still in the iris.
Trial and, uh, so that you know, working.
I think with this team from the
inginning was just as much I,
the fundamental
terior was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
beginning was just as much I,
You know,

in that context what I would say is, and there are a lot of people I. I'm just highlighting a few here to make a point and make a point in the context of aspire. You know, when we were designing, and as we've been conducting this study, we've been thinking about a lot of different things. As you'll hear about in a minute, you know what are the right outcomes? What can we learn about aspire beyond aspire? You know what are the relevant outcomes beyond our top line outcomes, and you can see here, you know,
Lauren Gaido, Alessandro Biffi.

I mean they've all had, I think, really key pieces of input into that and really unique perspectives.

You know, we didn’t choose, but you know, the current chair of the DSMB is Clark Haley.

So as many of you know, Clark Haley was very involved in the leadership of the original NINDS TPA trials, and it turns out that these historical things become relevant because you know what? For in a different context, when they were thinking about when they were looking at TPA and having
those very early DSMB meetings

for the NDS TPA trial,

they really had to think about this

balance of efficacy and hemorrhage,

bleeding and clotting in a very.

Sort of,

you know,

in an environment where they didn’t really

know that much from a clinical context,

and without you know sharing any sort

of insight information from the trial,

I think everybody would understand that.

You know when you’re thinking about aspire,

not just in the design,

but as the study goes along and

people start having endpoints clotting
endpoints or hemorrhaging points. These issues really come to the fore. I'll give you one concrete example. Oftentimes in a trial like this people will. Think about having a hemorrhage as a safety outcome. Why should it? Why shouldn’t hemorrhage only be a safety outcome? Why shouldn’t ischemia be a safety outcome? That’s a that’s if you think about safety as active harm. But if you think about ischemic stroke as sort of passive harm or passive safety endpoint, then ischaemia is can also
be considered a safety endpoint,

not just an efficacy endpoint.

And believe it or not,

some of these kinds of issues, really,

as we’ve learned during the course of

they’re not completely baked.

They really are something that you know.

Requires ongoing conversation,

so it’s been helpful to get all

these different perspectives.

Uhm, choice of drug.

So what really happens when

you think about the drug?

Well, I’ll tell you.

First of all,
And we went to the history that we had. And as we know in the last decade 15 years there have been a rush of a series of different no acts that have been used and proposed that have different profiles for administration, safety, efficacy etc. At the time when we were proposing the trial, of course apixaban. Had the what we thought was the safe, the best safety and efficacy profile, and the best recommendation from the American Heart Association for a FIB, at least at the time, and so that was a big part of it.
But there was another part of it too, which was that you know, this, uh, as we've heard earlier today, I think from Martin Landsberg, all of these trials cost a lot of money, and for those of you several on the call who are proposing trials, we're always trying to cut those costs as much as possible, and one of the places where there is a big ticket is in fact the study drug. From the 80 to the A1 admission
submissions was the ability to get the drug from Bristol Myers Squibb. You know, essentially at no cost or minimal cost, you know to the NININDS, and this comes up all the time. I'll tell you that we went around to every manufacturer of know acts at the time and asked them if they were interested and you know it was interesting. I mean, remember these patients have been excluded from. Every prior trial of anticoagulation and not only were they not interested, several of them told us look you use
our drug and you start to have safety events.

You may have lawsuits on your hand as well,

You know there's just a range of considerations that come up. I think when you're working with different manufacturers, different potential study drugs and you know we learned a lot at those early stages, so this is sort of what I mean by no choice of drug and no free lunch. You know, a lot of different sort of background background issues.
What when you end up supplying your own drug and this was the first time this had happened in stroke where we had a trial that had it for a prevention trial that where we had to secure our own medication outside of a sponsor sort of providing it for us. Well, if you’re coming up with your own drug, how are you going to come up with your own placebo? And that meant how do you design it? How do you know how closely should resemble the actual study drug? You know when you get the drug from a
sponsor, the sponsor owns the all the trademarks to the drug so they can really, truly make they're in a best position to make a matching placebo. When you go to a drug that still is not off patent and you have to make a placebo, there are issues come up about. Patents and trademarks actually so you have to, you know, somehow thread the needle to be able to get around those issues, but also be able to provide a matching placebo. So those are. Those are the kinds of things that we had to work through,
sort of at the beginning. What about choice of endpoints and choice of population so you know, we found this to be really interesting, and I think something that a lot of folks here have a lot of interest in. You know some of the prelim data that we had, and other groups have published really was. First of all, just codifying. What was I think essentially accepted sort of clinical question really wasn’t sort of showing efficacy versus you know, a background.
There’s an active comparator arm and the other piece of that is that you’re trying to figure out the difference between bleeding and clotting. And so traditionally, again, in stroke prevention trials, hard clinical endpoints like clinical events have been the main piece of what’s used for trial endpoints. In a sick population like brain hemorrhage survivors, certainly mortality comes into play. And we saw in our preliminary data that even when you looked at not low bar and non low bar patients that you know certainly these
endpoints were very important, but so was mortality. In fact, you can see that the association with a protective signal on mortality was actually quite robust. Acknowledging that all of these observation ull charities were likely highly confounded by virtue of their design. And you can see the point estimates for ischemic stroke very strong. Also, like in prior studies of anticoagulation, but nevertheless not nearly
00:13:05.442 --> 00:13:07.234 as strong as mortality.
NOTE Confidence: 0.896476471333333
00:13:07.240 --> 00:13:09.333 The other thing that you can see
NOTE Confidence: 0.896476471333333
00:13:09.333 --> 00:13:11.567 that was quite strong was actually
NOTE Confidence: 0.896476471333333
00:13:11.567 --> 00:13:13.677 the effect on functional outcome.
NOTE Confidence: 0.896476471333333
00:13:13.680 --> 00:13:15.955 And we thought functional outcome
NOTE Confidence: 0.896476471333333
00:13:15.955 --> 00:13:18.851 actually might be a really attractive
NOTE Confidence: 0.896476471333333
00:13:18.851 --> 00:13:21.566 endpoint for a prevention study,
NOTE Confidence: 0.896476471333333
00:13:21.570 --> 00:13:24.858 in part because it may have
NOTE Confidence: 0.896476471333333
NOTE Confidence: 0.896476471333333
00:13:26.510 --> 00:13:29.612 You know functional outcome and it
NOTE Confidence: 0.896476471333333
00:13:29.612 --> 00:13:32.635 is lesion and location naive, right?
NOTE Confidence: 0.896476471333333
00:13:32.635 --> 00:13:34.210 We don’t worry about whether
NOTE Confidence: 0.896476471333333
00:13:34.210 --> 00:13:35.470 or not it’s a
NOTE Confidence: 0.852922882222222
00:13:35.542 --> 00:13:37.877 small hemorrhage versus a large
NOTE Confidence: 0.852922882222222
00:13:37.877 --> 00:13:39.278 recurrent ischemic stroke.
NOTE Confidence: 0.852922882222222
00:13:39.280 --> 00:13:41.008 And in some sense, maybe neither

26
do patients what they care about is the disability that they're left.

So I'll tell you in our initial application to the NIH, we actually proposed functional outcome MRSI as the primary endpoint. Believe it or not from review was that funk that was thought to be sort of two different. I don't want to say two innovative but two different compared to prior stroke trials. So what we ended up doing is actually making it our key secondary and then reverting back to a more functional.
00:14:15.896 --> 00:14:18.158 traditional stroke endpoint.

NOTE Confidence: 0.852922882222222

00:14:18.160 --> 00:14:19.994 I'll finally end in the last couple

NOTE Confidence: 0.852922882222222

00:14:19.994 --> 00:14:21.701 of minutes here and and just tell

NOTE Confidence: 0.852922882222222

00:14:21.701 --> 00:14:22.997 you as many of you know,

NOTE Confidence: 0.852922882222222

00:14:22.997 --> 00:14:24.674 there have been other trials that

NOTE Confidence: 0.852922882222222

00:14:24.674 --> 00:14:26.759 have been going on around the world.

NOTE Confidence: 0.852922882222222

00:14:26.760 --> 00:14:29.840 Other phase two and phase three type studies.

NOTE Confidence: 0.852922882222222

00:14:29.840 --> 00:14:31.484 This was one that was published

NOTE Confidence: 0.852922882222222

00:14:31.484 --> 00:14:33.130 just recently in Lancet Neurology,

NOTE Confidence: 0.852922882222222

00:14:33.130 --> 00:14:36.420 an open label RCT in the UK.

NOTE Confidence: 0.852922882222222

00:14:36.420 --> 00:14:38.676 Lots of similarities, lots of differences.

NOTE Confidence: 0.852922882222222

00:14:38.680 --> 00:14:41.158 There was an open label design

NOTE Confidence: 0.852922882222222

00:14:41.160 --> 00:14:43.036 they were looking at.

NOTE Confidence: 0.852922882222222

00:14:43.036 --> 00:14:45.381 Non inferiority of anticoagulation and

NOTE Confidence: 0.852922882222222

00:14:45.381 --> 00:14:48.569 the comparison group had either aspirin.

NOTE Confidence: 0.852922882222222

00:14:48.570 --> 00:14:51.630 Or no anti thrombotic.
Ultimately they were underpowered to look at any efficacy endpoint. And they had a figure in their paper that showed the numerical differences between various endpoints, and I draw your attention away from the bleeding and clotting because we know ultimately, these were small numbers, none of which had significance, but something that we had been paying a lot of attention to, and that we continue to do so.

Which was that, you know, mortality was a part of our primary
00:15:21.373 --> 00:15:23.920 endpoint for a number of different reasons,
NOTE Confidence: 0.852922882222222

00:15:23.920 --> 00:15:26.954 including the strong effect size combined
NOTE Confidence: 0.852922882222222

00:15:26.954 --> 00:15:29.866 with the feasibility of what we needed to.
NOTE Confidence: 0.852922882222222

00:15:29.870 --> 00:15:32.005 To propose in order to get a
NOTE Confidence: 0.852922882222222

00:15:32.005 --> 00:15:33.938 study funded and to go forward.
NOTE Confidence: 0.852922882222222

00:15:33.940 --> 00:15:35.176 But you know,
NOTE Confidence: 0.852922882222222

00:15:35.176 --> 00:15:38.060 we’re very mindful of the fact that
NOTE Confidence: 0.852922882222222

00:15:38.060 --> 00:15:40.444 all causes of death are not the same,
NOTE Confidence: 0.852922882222222

00:15:40.450 --> 00:15:42.730 and all of them may or may not
NOTE Confidence: 0.852922882222222

00:15:42.730 --> 00:15:44.669 be modified by anticoagulation.
NOTE Confidence: 0.852922882222222

00:15:44.670 --> 00:15:45.828 And I think you know this.
NOTE Confidence: 0.852922882222222

00:15:45.830 --> 00:15:48.410 This figure may support that.
NOTE Confidence: 0.852922882222222

00:15:48.410 --> 00:15:50.570 That’s a potential concern going forward,
NOTE Confidence: 0.852922882222222

00:15:50.570 --> 00:15:53.041 so that’s something that I think that
NOTE Confidence: 0.852922882222222

00:15:53.041 --> 00:15:55.457 will all continue to pay attention to.
NOTE Confidence: 0.852922882222222

00:15:55.460 --> 00:15:58.016 Those are some of the aspects that went into.
Ultimately, what are our overall aspiring’s, which I think you know, which is to really look to see if apixaban is superior or aspirin in a double blind design on traditional stroke endpoints. But we are going to pay a lot of attention to outcomes like the modified Rankin and and other outcomes. I think everyone is familiar with and you know, for those of you who are on the call where we’ve launched this one campaign. And in honor of U2 and Bono,
for those of you who are from that generation, and you know, we're hoping every center will be able to just put in one. So I think I'm towards the end of my time. But if there's time for questions, I'd be happy to answer any that you might have. Thank you so much Kevin. I don't see any questions in the chat box. I think if anyone has any questions please type them in the chat box or feel free to reach out Doctor Chat afterwards. I think for the interest of time it's 115. I will move on to the next speaker.