WEBVTT

1
00:00:01.700 --> 00:00:02.390
Drew Kasper: And

2
00:00:06.660 --> 00:00:07.600
Drew Kasper: great

3
00:00:11.440 --> 00:00:21.500
Drew Kasper: good morning and welcome to the new technology. Add on payment or ntap. Town Hall for fiscal year 2026.

4
00:00:28.270 --> 00:00:35.450
Drew Kasper: I'm your host drew Casper with the division of new technology and the center for Medicare's Technology coding and pricing group.

5
00:00:35.810 --> 00:01:05.450
Drew Kasper: Thank you all for being with us today. We are excited to be hearing from and interacting with you all in today's event. Before we begin, I'd like to cover some basics for today's meeting. In the event, we experience any major technical issues you can reach out via email to the Newtek mailbox, which many of you are already familiar with. I'm sure it's NEWT. ECH. Or newtek@cmshhs.gov.

6
00:01:05.720 --> 00:01:12.979
Drew Kasper: and we will do our best to keep you apprised of what's happening in the interest of

7
00:01:13.530 --> 00:01:32.389
Drew Kasper: data, volume, and bandwidth. With such a large group of people, the standard for today will be to not activate your video unless you are presenting presenters are welcome to activate your camera during your presentation. Otherwise we'd appreciate it if you would not activate your cameras.

8
00:01:33.420 --> 00:01:48.569
Drew Kasper: Attendees may submit their questions using the Q&A feature at the bottom of the screen, or by using the raised hand feature in zoom. If you raise your hand, we can enable you to unmute yourself during the Q. And a. Sessions

9
00:01:48.850 --> 00:02:10.390
Drew Kasper: for public attendees who are only dialed in by telephone. You'll need to email your questions to the Cms new tech email box again. That's NEWT. ech@cms.hhs.gov, I'll be monitoring the mailbox throughout the session questions for presenters should pertain to the substantial clinical improvement

10
00:02:10.699 --> 00:02:36.170
Drew Kasper: of the technology presented. We sometimes refer to substantial clinical improvement under the acronym sci. As a reminder. There are 3 main criteria for new technology, add-on payment, eligibility, newness, cost and substantial clinical improvement over existing services or technologies. We're here today to talk about the substantial clinical improvement criterion specifically

11
00:02:37.580 --> 00:03:00.479
Drew Kasper: for Cms's consideration in the Ipps proposed rule. Public comments must be submitted to Cms. In writing via email to newtek@cms.hhs.gov. With the subject line, Town Hall comment, followed by the technology name. All comments must be received by 5 Pm. Eastern Standard time on Monday, December 16.th

12
00:03:00.820 --> 00:03:14.739
Drew Kasper: If you raise a verbal comment during the Town Hall today during the Q. And a segments after each presentation, please remember, you still must send the written comment to ensure consideration in the proposed rule.

13
00:03:15.160 --> 00:03:20.918
Drew Kasper: You'll see this information also about submitting comments at the bottom of the agenda

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00:03:21.989 --> 00:03:26.780
Drew Kasper: I wanted to mention also our comment period opens up

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00:03:28.070 --> 00:03:51.469
Drew Kasper: after the Town Hall and goes through that time I mentioned 5 Pm. On Monday, December 16.th So if anyone submitted comments on these presentations and sci prior to the Town Hall to our new tech mailbox. Please do resubmit them. I sent everyone back who had identified

16

00:03:51.580 --> 00:03:57.728
Drew Kasper: the email as a as a comment related to the Town Hall that they please do

17
00:03:58.710 --> 00:04:06.469
Drew Kasper: resubmit it to us after the Town Hall. That's the actual open period for comments on the Town Hall and Sci.

18
00:04:08.230 --> 00:04:36.929
Drew Kasper: just to clarify. That is different from the Nprm comment period. The notice of proposed rulemaking that gets published around April first, st there is a 60 day comment period on the entire rule. That's different than this is just a comment period for the Town Hall. We'll head right into our presentation from the division of new technology team this morning, starting with the director of the Division of new technology. Allison, Pompei.

19
00:04:37.180 --> 00:04:41.099
Drew Kasper: Alison, go ahead and unmute and take it away. Thanks.

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00:04:41.340 --> 00:04:44.059
Allison Pompey: Can you hear me? Am I unmuted? Properly.

21
00:04:44.400 --> 00:04:45.770
Drew Kasper: Yes, we can hear you. Thanks.

22
00:04:45.770 --> 00:04:59.390
Allison Pompey: Wonderful. Good morning, everyone. And welcome again. I'm Alison Pompey, as you mentioned, Director of New Technology, which is the division that houses the Ntap program.

23
00:04:59.840 --> 00:05:21.700
Allison Pompey: And, as Drew briefly mentioned, it's been really informative for our team to read your applications, and we're really excited to hear more from you about how your technologies pose a substantial clinical improvement for medicare beneficiaries compared to what's currently available. But before we delve into the presentations, I want to take a few minutes to discuss

24
00:05:21.700 --> 00:05:36.600
Allison Pompey: some of the steps we, the Ntap team, are taking to provide additional insight into our internal processes, to improve our

program and to move forward with ntap applicants in a more proactive way, based on some of the trends we're seeing.

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00:05:36.810 --> 00:05:48.250
Allison Pompey: So moving forward and actually starting with this town Hall. We're including a new section on the Town Hall agenda. The very next section which members of the Ntap team will discuss.

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00:05:48.510 --> 00:05:53.109
Allison Pompey: That section is geared towards providing insight into best practices

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00:05:53.510 --> 00:06:12.529
Allison Pompey: related to how we analyze sci information applicants provide against the ntap sci criteria, the types of information and level of detail that could be submitted to support an sci claim and other issues pertaining to sci or operational concerns that could affect

28
00:06:12.610 --> 00:06:31.709
Allison Pompey: the analysis and approval of ntap applications. So what do we hope to get from that? Well, we hope that these discussions will make it easier to understand what to include in the initial ntap application as well as in supplemental materials, such as what you would be submitting after this town hall.

29
00:06:31.860 --> 00:06:44.339
Allison Pompey: and we hope that these discussions will lead to prompt submission of ntap related applications, such as the Icd 10 coding applications that go along in some cases with the ntap application.

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00:06:44.600 --> 00:06:51.310
Allison Pompey: which could, you know, minimize potential for disruptions and and tap payment for approved applications.

31
00:06:51.580 --> 00:07:16.789
Allison Pompey: And further, we believe that these measures will also support our current policies, for example, our policy to publicly post some application materials. And so, as applicants think through what Cms really needs to evaluate application. Perhaps these discussions will result in decreased submission of extraneous information in favor of more concise information that demonstrates

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00:07:17.080 --> 00:07:29.709
Allison Pompey: technology superiority to currently available technologies, that in turn, we believe, may also make it easier for the public as they review the ntap postings for comment.

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00:07:29.890 --> 00:07:55.900
Allison Pompey: So in addition to that section on the Town Hall agenda, we're exploring additional measures to support potential applicants prior to the ntap submission, deadline. So please keep checking our webpage for updates as we approach the next and subsequent application cycles to see what other measures we may have available to you.

34
00:07:56.110 --> 00:08:00.879
Allison Pompey: so without further ado, I will turn it over to the Ntap team.

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00:08:04.120 --> 00:08:22.889
Lily Yuan: Thank you, Allison, so good morning, all. So we would like to provide a quick refresher on the substantial clinical improvement criterion sci and share some notes on what we are looking for when reviewing applications for this criterion, and what we've observed from applications submitted in the past.

36
00:08:23.390 --> 00:08:49.279
Lily Yuan: Our goal here is to share this information, to help applicants understand how to demonstrate that their technology meets the sci criterion to limit concerns that need to be raised in our notice of proposed rulemaking, and to help applicants provide Cms. With the relevant information to make the sci assessments and to the extent possible. Some of this relevant information as a part of the initial application submission

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00:08:49.980 --> 00:09:02.999
Lily Yuan: overall. We want to provide a reminder that while FDA has regulatory responsibility for decisions related to marketing authorization. We do not rely on FDA criteria. In our evaluation of sci.

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00:09:03.110 --> 00:09:16.949
Lily Yuan: The sci criterion does not depend on the standard of safety and effectiveness on which FDA relies, but rather on a demonstration of Sci and the Medicare population as demonstrated in our regulations

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00:09:17.160 --> 00:09:25.879
Lily Yuan: as provided on the slide. There are 3 ways to demonstrate that a technology represents a substantial clinical improvement under our regulations.

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00:09:26.080 --> 00:09:37.950
Lily Yuan: Under the 1st wave a. The new technology offers a treatment option for a patient population unresponsive to or ineligible for currently available treatments.

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00:09:38.250 --> 00:09:55.510
Lily Yuan: For an applicant. To make this assertion, the applicant should demonstrate that currently available standard of care treatments cannot be used in the patient population or the applicant should identify a specific subpopulation that is unresponsive to available treatments.

42
00:09:55.700 --> 00:10:05.210
Lily Yuan: It is not enough for the technology to be a better option for patients to manage the disease, which instead falls under assertion. C.

43
00:10:05.780 --> 00:10:22.999
Lily Yuan: In addition, we often have applicants assert that they meet this criterion by stating that their technology is 1st in class or new, that there is no consensus for treatment of the disease, and or that some patients don't respond well to a particular treatment.

44
00:10:23.190 --> 00:10:34.269
Lily Yuan: Along with those assertions, we have received background evidence to state that there isn't a standard of care for the disease, or that patients with the disease have poor outcomes.

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00:10:34.410 --> 00:10:45.310
Lily Yuan: However, if there are other existing treatments that these patients can use regardless of outcomes, then we are unable to determine sci. Under this assertion

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00:10:45.490 --> 00:10:59.759
Lily Yuan: we further note that mechanism of action and units are not relevant to the assessment of sci instead, technologies must be

compared to all treatments used for these patients and not just similar technologies.

47
00:11:00.690 --> 00:11:29.860
Lily Yuan: So under the second way to demonstrate Scib, the new technology offers the ability to diagnose a medical condition in a patient population where that medical condition is currently undetectable, or offers the ability to diagnose a medical condition earlier in a patient population than allowed by currently available methods. And there must also be evidence that use of the new technology to make a diagnosis affects the management of these patients.

48
00:11:30.330 --> 00:11:37.299
Lily Yuan: So under the assertion, all aspects must equally are equally necessary to demonstrate, for sei

49
00:11:37.660 --> 00:11:48.610
Lily Yuan: applicants must demonstrate both that the condition is diagnosed earlier, or that it can now be detected, and that this diagnosis changes the management of the patients.

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00:11:48.850 --> 00:11:58.099
Lily Yuan: Specifically, we assess, if the evidence demonstrates that use of the technology is directly linked to a change in patient management.

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00:11:58.770 --> 00:12:16.570
Lily Yuan: For example, we may receive evidence from applicants that rely on an inferred outcome that a technology allows for an earlier diagnosis of a condition along with background papers stating that earlier diagnosis allows for earlier treatments of the condition.

52
00:12:16.850 --> 00:12:23.630
Lily Yuan: However, this doesn't demonstrate that the technology would actually allow for earlier treatment. In practice.

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00:12:23.820 --> 00:12:32.879
Lily Yuan: We would like to see evidence such as studies or case reports that demonstrate how the technology directly resulted in earlier treatments

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00:12:33.870 --> 00:12:52.080
Lily Yuan: and under the final way to demonstrate sci assertion. C. The use of the new technology significantly improves clinical outcomes relative to services or technologies previously available. The regulations list, the following as outcomes that could demonstrate sci next slide, please.

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00:12:55.260 --> 00:13:06.050
Lily Yuan: So one a reduction in at least one clinically significant adverse events, including a reduction in mortality or a clinically significant complication.

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00:13:06.290 --> 00:13:13.139
Lily Yuan: 2. A decreased rate of at least one. Subsequent diagnostic or therapeutic intervention.

57
00:13:13.650 --> 00:13:19.500
Lily Yuan: 3. A decreased number of future hospitalizations for physician visits.

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00:13:19.910 --> 00:13:30.330
Lily Yuan: 4. A more rapid beneficial resolution of the disease process, treatments, including, but not limited to a reduced length of stay or recovery time.

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00:13:30.660 --> 00:13:35.399
Lily Yuan: 5. An improvement in one or more activities of daily living.

60
00:13:35.570 --> 00:13:43.259
Lily Yuan: 6. An improved quality of life, and 7. A demonstrated greater medication. Adherence for compliance.

61
00:13:43.590 --> 00:14:11.189
Lily Yuan: Under this assertion applicants claims should relate to a demonstration of one of the 7 outcomes listed rather than claims regarding physiological changes or other surrogate measures, while applicants sometimes provide background articles to explain why a particular physiological change or measure is clinically relevant because it leads to a particular outcome. This does not demonstrate that the technology itself changed the outcome.

62

00:14:11.470 --> 00:14:20.809
Lily Yuan: In addition, stating that a technology is safe and or effective, does not demonstrate an improved outcome for the purposes of sci.

63
00:14:21.460 --> 00:14:37.620
Lily Yuan: And finally, we wanted to provide a note for future Town Hall meetings. Our general recommendation is to focus the majority of the presentation on how the new technology meets the fci criterion and keeping the background information to a minimum such as one to 2 min.

64
00:14:37.940 --> 00:14:51.460
Lily Yuan: We greatly appreciate your attendance at this Town Hall, and the opinions and presentations provided today will assist us as we evaluate sci for these new technology applications. So now I'll turn it back to our host. Drew.

65
00:14:57.000 --> 00:15:10.839
Drew Kasper: Great. Thank you so much, Lily. We hope that this was helpful as we approach the supplemental information deadline, and perhaps especially for those of you who may be working with ntap applications next year, and in future years.

66
00:15:12.110 --> 00:15:31.320
Drew Kasper: As a reminder, all attendees may submit their questions, using the QA. Feature at the bottom of the screen, or you can use the raise hand feature in zoom, and we will enable you to unmute and ask your question verbally for those who are dialed in by phone. You'd need to email your questions to the Cms. Newtek email box at

67
00:15:31.540 --> 00:15:39.150
Drew Kasper: New Tech, NEWT. ech@cms.hhs.gov.

68
00:15:40.410 --> 00:15:58.739
Drew Kasper: We will now move on to the fiscal year 2026 ntap application presenters. I'd like to remind the presenters that we have allotted exactly 10 min for each presentation, after which we'll have questions from the public and then from Cms. With responses, from presenters.

69
00:15:58.870 --> 00:16:06.029
Drew Kasper: we will advance the slides for each presentation, and presenters should indicate when to advance to the next slide

70
00:16:08.120 --> 00:16:15.109
Drew Kasper: without further ado. We'll now hear from the presenters, for our castle.

71
00:16:15.320 --> 00:16:21.930
Drew Kasper: also known as Obicapta gene auto. Lucelle. You may now unmute your phone and introduce yourself.

72
00:16:22.670 --> 00:16:36.700
Bijal D. Shah: Thank you. Hi. My name is Dr. Bejelshaw, from the Moffitt Cancer Center on behalf of myself, my colleagues, and the team at Autilus. Thanks for inviting us to share these data on Acatsl or Opicel for the treatment of relapse and refractory B-cell all next slide.

73
00:16:38.580 --> 00:16:40.830
Bijal D. Shah: These are my disclosures.

74
00:16:41.070 --> 00:16:42.040
Bijal D. Shah: Next slide.

75
00:16:45.230 --> 00:16:47.690
Bijal D. Shah: A catsule is novel.

76
00:16:47.890 --> 00:16:55.890
Bijal D. Shah: its delivery is innovative, and the findings are clinically significant. As I'll share with you. Throughout this presentation

77
00:16:56.240 --> 00:17:04.520
Bijal D. Shah: this is the 1st car T cell therapy to be approved without an accompanying rems program.

78
00:17:04.900 --> 00:17:10.729
Bijal D. Shah: a reflection of the safety in with the use of this product.

79
00:17:11.490 --> 00:17:29.210
Bijal D. Shah: These data are based on the pivotal Felix Trial, as

recently published in the New England Journal of Medicine. This reflects the largest and most diverse population of car T-cell therapy for relapsed and refractory, all including for those over the age of 65. Next slide.

80
00:17:33.000 --> 00:17:35.030
Bijal D. Shah: Although this is a background slide.

81
00:17:35.260 --> 00:17:48.279
Bijal D. Shah: I think it's a very important one. It frames the discussion for everything I'll be talking about later, and I think, also reflects my enthusiasm for this particular car t cell therapy.

82
00:17:50.180 --> 00:18:00.140
Bijal D. Shah: Older adults, or those over the age of 65 will comprise around 14% of newly diagnosed all in the United States.

83
00:18:02.660 --> 00:18:09.929
Bijal D. Shah: These same individuals have higher toxicity with any therapy that we deliver

84
00:18:11.060 --> 00:18:24.199
Bijal D. Shah: and lower response rates due to the underlying biology of their leukemia, often accompanied by things such as Tp. 53. Loss, and so on.

85
00:18:26.160 --> 00:18:40.010
Bijal D. Shah: These individuals are generally transplant, ineligible for all of these same reasons. And so car t-cell therapy has become an important part of that paradigm for therapy.

86
00:18:40.780 --> 00:18:41.870
Bijal D. Shah: However.

87
00:18:42.120 --> 00:18:57.209
Bijal D. Shah: we have to recognize that current car T cell therapies are associated with a high rate of acute toxicity, including upwards of a 30% rate of high-grade neurologic symptoms.

88
00:18:57.750 --> 00:19:06.380
Bijal D. Shah: This acute toxicity translates into longer

hospitalizations and an increased need for rehab

89
00:19:06.940 --> 00:19:15.900
Bijal D. Shah: and skilled nursing placement. Following the delivery of car T cell therapy. So a car T product that comes with lower rates

90
00:19:16.690 --> 00:19:23.919
Bijal D. Shah: of Crs and Icanns provides a significant clinical improvement

91
00:19:24.430 --> 00:19:28.680
Bijal D. Shah: for this otherwise vulnerable population. Next slide.

92
00:19:31.820 --> 00:19:34.780
Bijal D. Shah: as I shared Akatzel is novel.

93
00:19:35.440 --> 00:19:39.850
Bijal D. Shah: The binder is part of what makes this product safer.

94
00:19:40.310 --> 00:19:55.439
Bijal D. Shah: It is a low affinity binder to CD. 19, and as a consequence, the engagement of T cells is more physiologic, we see less cytokine production, and accordingly less toxicity.

95
00:19:56.350 --> 00:20:05.069
Bijal D. Shah: We also get with this same physiologic binding enhanced persistence.

96
00:20:06.340 --> 00:20:09.899
Bijal D. Shah: Why? Because the T cells are not driven to exhaustion.

97
00:20:11.980 --> 00:20:23.459
Bijal D. Shah: We build on this with a 4 1 bb. Domain to further enhance the central memory and T naive enrichment of the product, and again build on this concept of persistence. And then

98
00:20:24.520 --> 00:20:27.859
Bijal D. Shah: comes the innovation, which is the delivery.

99

00:20:28.460 --> 00:20:33.140
Bijal D. Shah: This is also the 1st car T to be approved.

100
00:20:33.340 --> 00:20:42.709
Bijal D. Shah: using a tumor burden, guided dosing approach with a split infusion, as I will show you on the next slide

101
00:20:43.670 --> 00:20:44.450
Bijal D. Shah: next.

102
00:20:47.460 --> 00:20:54.619
Bijal D. Shah: Here you see the delivery mechanism. This is a single treatment with a split dose

103
00:20:54.900 --> 00:21:08.950
Bijal D. Shah: for those with low tumor burden. They get a higher priming dose, followed by the second dose to complete the infusion, whereas those with higher tumor burden receive a lower priming dose before the second infusion.

104
00:21:11.490 --> 00:21:18.669
Bijal D. Shah: This approach allows us to mitigate toxicity

105
00:21:19.130 --> 00:21:30.939
Bijal D. Shah: and see preserved expansion, and when I say this, I want to go a step further. This is the this. With this product we see a Pk

106
00:21:32.960 --> 00:21:36.090
Bijal D. Shah: showing that expansion is identical.

107
00:21:36.670 --> 00:21:43.099
Bijal D. Shah: or I should even say, higher in patients with high tumor burden, something we have not seen

108
00:21:43.890 --> 00:21:47.599
Bijal D. Shah: with other car T cells in this same space next slide.

109
00:21:50.010 --> 00:21:59.740
Bijal D. Shah: Now comes the fun parts. We enrolled 127 patients. 20%

of those were over the age of 65.

110
00:21:59.900 --> 00:22:03.160
Bijal D. Shah: These patients are heavily pretreated, as we might expect

111
00:22:03.550 --> 00:22:07.619
Bijal D. Shah: with meaningful tumor burden at the time of infusion next slide.

112
00:22:10.820 --> 00:22:12.000
Bijal D. Shah: And here it is.

113
00:22:13.360 --> 00:22:20.370
Bijal D. Shah: The novelty and innovation of this particular product have led have culminated

114
00:22:20.830 --> 00:22:26.829
Bijal D. Shah: in extraordinarily low rates of cytokine release syndrome and neurologic symptoms.

115
00:22:28.210 --> 00:22:39.250
Bijal D. Shah: Again, the comparator being showing rates in the 30 percentile range for high grade neurologic complications.

116
00:22:40.140 --> 00:22:44.160
Bijal D. Shah: This is clinically meaningful. Next slide.

117
00:22:48.170 --> 00:22:58.319
Bijal D. Shah: Some sites speak for themselves, and I'm excited by this one as well. Focusing on our patients, 65 and older, the response rate was nearly 100%.

118
00:23:00.680 --> 00:23:08.060
Bijal D. Shah: So when we take into account that disease biology that I shared with you earlier, we get to see how this and that this therapy is impactful in that population

119
00:23:08.160 --> 00:23:09.080
Bijal D. Shah: next slide.

120
00:23:12.220 --> 00:23:17.540
Bijal D. Shah: It is not just a high response rate. These responses appear durable.

121
00:23:18.210 --> 00:23:24.799
Bijal D. Shah: and we can now see with extended follow-up, that the

122
00:23:24.920 --> 00:23:31.770
Bijal D. Shah: addition of subsequent transplant may not meaningfully improve outcomes.

123
00:23:32.610 --> 00:23:34.380
Catherine Bernstein: You have 3 min remaining.

124
00:23:34.380 --> 00:23:35.080
Bijal D. Shah: Thank you.

125
00:23:35.190 --> 00:23:46.819
Bijal D. Shah: This suggests that the persistence and the biological biological activity of this car T product may allow for extended

126
00:23:47.660 --> 00:23:54.450
Bijal D. Shah: clinical improvement next slide, please, and that's depicted here.

127
00:23:55.110 --> 00:24:01.780
Bijal D. Shah: 40% of the patients are in ongoing continuous complete remission without any subsequent therapy.

128
00:24:03.870 --> 00:24:12.990
Bijal D. Shah: This is especially important for our patients over the age of 65 who are unlikely to be candidates for subsequent stem cell transplant.

129
00:24:16.220 --> 00:24:17.150
Bijal D. Shah: Next slide.

130
00:24:19.980 --> 00:24:26.640

Bijal D. Shah: In conclusion, a cattle is novel by virtue of its binder.

131
00:24:28.630 --> 00:24:37.190
Bijal D. Shah: It is innovative by virtue of its delivery, and it has generated significant clinical improvement

132
00:24:37.350 --> 00:24:40.340
Bijal D. Shah: as demonstrated here by its safety.

133
00:24:41.650 --> 00:24:49.660
Bijal D. Shah: particularly for our patients over the age of 65, where these same toxicities are more likely to culminate in considerable

134
00:24:50.080 --> 00:25:04.550
Bijal D. Shah: complications, including prolonged hospitalization. And again, the need for subsequent advanced care. Beyond that hospital stay efficacy is preserved

135
00:25:04.970 --> 00:25:11.720
Bijal D. Shah: with a possible plateau in survival, suggesting, we can also forego transplant, which is important

136
00:25:12.250 --> 00:25:14.690
Bijal D. Shah: in those patients who may be transplant ineligible.

137
00:25:15.230 --> 00:25:18.799
Bijal D. Shah: With that I want to thank you, and I'll take questions.

138
00:25:22.670 --> 00:25:27.061
Drew Kasper: Great. Thank you very much for your presentation.

139
00:25:28.030 --> 00:25:36.010
Drew Kasper: Are there any questions from the public? This may include other applicants. We'll take questions for Cms. After this

140
00:25:36.300 --> 00:25:38.010
Drew Kasper: any questions from the public.

141

00:25:43.540 --> 00:25:47.190
Drew Kasper: not seeing any questions entered into the Q. And a.

142
00:25:50.720 --> 00:25:58.280
Drew Kasper: I'm not seeing any hands raised from our attendees or other panelists.

143
00:26:00.160 --> 00:26:03.030
Drew Kasper: Something has come through in the Q. And A.

144
00:26:05.220 --> 00:26:08.209
Drew Kasper: Howard has asked cost savings.

145
00:26:09.210 --> 00:26:14.499
Drew Kasper: which I think is to say, you know, do you anticipate that this would generate cost savings.

146
00:26:14.850 --> 00:26:32.060
Bijal D. Shah: I do we presented at. I'm actually still in San Diego at our annual meeting here just yesterday, I think, or 2 days ago. Sorry the healthcare resource utilization. And it's a reflection mainly of hospitalization time.

147
00:26:32.060 --> 00:26:47.770
Bijal D. Shah: So for those patients who required extended hospitalization due to these adverse events, the added cost for neurologic complications was around. Just the hospitalization costs were around 40, something. 41,000, if I recall.

148
00:26:47.970 --> 00:27:02.899
Bijal D. Shah: added costs for Cytokine release syndrome were also in the 20 plus $1,000 range. So this is meaningful in terms of the cost savings related to these lower rates of high-grade toxicity. So yes.

149
00:27:07.475 --> 00:27:10.730
Drew Kasper: Any any other questions from the public.

150
00:27:10.730 --> 00:27:11.480
Bijal D. Shah: Company.

151

00:27:14.770 --> 00:27:20.290
Drew Kasper: No additional questions in the Q. And A. At this time there are no hands raised.

152
00:27:22.020 --> 00:27:26.490
Drew Kasper: and there are no questions in the Cms. New tech mailbox.

153
00:27:27.900 --> 00:27:34.080
Drew Kasper: Okay? So with that, we'll move on to questions from Cms.

154
00:27:34.380 --> 00:27:38.269
Drew Kasper: Please unmute your phone to ask questions, questions from Cms.

155
00:27:39.680 --> 00:28:08.239
Sophia Chan: Hi, Dr. Shah, thank you so much for the presentation. This is Sophia Chan Cms. I'm wondering, in one of the charts you mentioned, that for those with high tumor burden they had an eye counts incidence rate of 15%. How does this compare to other available car t-cell therapies for patients with comparable tumor burden and an advanced age.

156
00:28:08.410 --> 00:28:30.150
Bijal D. Shah: No, that's a very good question. What we saw with Brexasel, which is the other approved product in this population, was in those with very high tumor burden. It was around 10%. But I have to qualify that a little bit, Sophia. That's because we didn't see expansion in those patients who had very high tumor burden.

157
00:28:30.390 --> 00:28:54.239
Bijal D. Shah: And so when we look to, I guess the closest I can compare it to is a mantle cell or large B cell lymphoma, where we also have similar products. When we talk about using car t cell therapy in those patients with advanced tumor burden, the high grade icans rate is again around the 30 percentile range.

158
00:28:54.450 --> 00:29:06.999
Bijal D. Shah: When we talk about those 65 and older. And also we presented at this year's annual Congress, our data with real world outcomes. This is the Roca collaboration that I'm a part of.

159
00:29:07.190 --> 00:29:17.530

Bijal D. Shah: And we could show that it was around a 30% rate of high-grade Icans in adults, with all using the Brexasel product

160
00:29:17.820 --> 00:29:27.870
Bijal D. Shah: across the board. And in this case the I'm trying to remember the interaction with tumor burden. I apologize. I'm just. I'm going from memory here. But I

161
00:29:27.970 --> 00:29:31.660
Bijal D. Shah: my recollection is that in this analysis

162
00:29:31.850 --> 00:29:53.699
Bijal D. Shah: we saw that it was around a 30% rate of high-grade icans, independent of tumor burden. So, as I mentioned on trial with Brexasel, the rates were low, but in the real world setting we are seeing higher grade Icans for me, Sophia. The main challenge with that as I shared, is when we see it. We

163
00:29:53.780 --> 00:30:08.649
Bijal D. Shah: really are looking at extended hospital stays. I don't know why, but when we see high-grade Icans, these patients get very, very debilitated when I say debilitated to the point where you know, touching the finger to nose becomes a challenge.

164
00:30:08.710 --> 00:30:31.359
Bijal D. Shah: It's unlike anything I've seen. I suspect it's a reflection of just the severity of inflammation, coupled with, you know, being bed bound for a few days, but it is very common in that circumstance to need to extend the hospitalization to allow for physical therapy, occupational therapy speech therapy to make sure that they can swallow to avoid those aspiration pneumonias that follow.

165
00:30:31.430 --> 00:30:37.270
Bijal D. Shah: and then often like, I said, as I mentioned rehab and skilled nursing, but afterwards, so this is

166
00:30:37.380 --> 00:30:44.430
Bijal D. Shah: that nuance that I'm that I'm hopefully, successfully communicating, as relates to my excitement around a lower toxicity product.

167

00:30:45.290 --> 00:30:54.360
Sophia Chan: I see. So do you have any data comparing Orcazil to existing treatments that are not party therapies?

168
00:30:55.983 --> 00:30:57.990
Bijal D. Shah: So the

169
00:30:59.340 --> 00:31:11.049
Bijal D. Shah: the answer is head to head. No, because this was a single arm. Phase 2. When we talk about what's currently FDA approved. In this space we have only 3 options blinitumumab.

170
00:31:11.380 --> 00:31:18.649
Bijal D. Shah: where the expected durable benefit in this patient population is around 20%

171
00:31:18.800 --> 00:31:29.499
Bijal D. Shah: for relapsed refractory disease. It was explored in patients with newly diagnosed disease. However, those patients, 55 and older, did not show any significant benefit with the incorporation of Blena.

172
00:31:29.920 --> 00:31:44.589
Bijal D. Shah: And so you know, this seems to provide advantage over that particular therapeutic approach. Inotuzumab is also being explored in older, patient populations. I think we're still learning the challenge with Inotuzumab is its toxicity.

173
00:31:44.590 --> 00:32:00.289
Bijal D. Shah: The coleachomycin binder seems to come with considerable cytopenia, so you know, it's 1 of these where you have to pay very close attention to the curves, because we'll show this beautiful sort of disease specific survival. But when you look at overall survival, it's much worse due to the complication

174
00:32:01.390 --> 00:32:02.830
Bijal D. Shah: that are associated with that.

175
00:32:02.960 --> 00:32:06.359
Bijal D. Shah: I think that we're going to start to see

176

00:32:06.890 --> 00:32:34.729
Bijal D. Shah: trials. There was one, the cooperative group study of blinatumumab and Intuzumab, so sequential in older adults. With all this was a frontline study. So this is a little bit different than this setting. But in that patient population it was around 50% survival at 2 years, which is where we are here with this product in the relapsed refractory setting. So I think that as it relates to comparable therapies. This is a significant clinical improvement.

177
00:32:35.340 --> 00:32:44.879
Bijal D. Shah: I don't know if you were asking about a comparison to Brexasel in terms of the the clinical activity. I hope I've communicated the safety being the big differentiator. There.

178
00:32:46.380 --> 00:32:56.080
Sophia Chan: Okay, I see. Thank you. And lastly, what I I saw that for some of the patients who received Octa cell

179
00:32:56.200 --> 00:33:08.749
Sophia Chan: afterwards they also went on to receive stem cell transplant, but some did not. So what were the factors that went into the decisions.

180
00:33:09.280 --> 00:33:33.760
Bijal D. Shah: You know that analysis is ongoing. There were a total of 18 out of the 127 that went to subsequent transplant. So it was a minority of the patients. It was at the physician's discretion. And so it is part of what we're trying to delineate. It was, as you might imagine, predominantly younger patients predominantly. Those that were transplant naive around 40% of the patients who came on to study had already seen a transplant.

181
00:33:34.110 --> 00:33:54.539
Bijal D. Shah: And so, you know, I think that I can only tell you that that work is ongoing. It's hard to split 18 patients up into too many different categories with the significant data we are within our Roca collaboration. We've actually already decided that we'll be moving forward to also try to understand how obacel functions in the real world with

182
00:33:54.660 --> 00:34:15.409
Bijal D. Shah: even larger data sets to try and help us understand again what's driving some of that in terms of the responsiveness that was not a factor. The patients who went on to transplant were Mrd

negative. And so that wasn't that they were being driven to transplant because of some poor therapeutic outcome. I suspect it was just again investigator discretion based on something that they were seeing.

183
00:34:16.580 --> 00:34:18.900
Sophia Chan: I see. Thank you so much.

184
00:34:18.909 --> 00:34:19.309
Bijal D. Shah: You're welcome.

185
00:34:19.310 --> 00:34:20.930
Sophia Chan: I don't have further questions.

186
00:34:24.429 --> 00:34:38.939
Adina Hersko: Hi, thank you, for my name is Adina Hersko with Cms. Can you explain how the tumor burden guided dosing that you're talking about is different from split dosing or step up dosing. Seen with other car t therapies.

187
00:34:39.599 --> 00:34:53.719
Bijal D. Shah: So again, and you'll have to help me out, Adina. I don't know of any other approved cartes that are using step-up dosing so again, at least with what I do. We work with the approved products, lysocel

188
00:34:53.829 --> 00:34:59.119
Bijal D. Shah: brexacel, accessell tsecl. And and now, obacel.

189
00:34:59.429 --> 00:35:08.309
Bijal D. Shah: this is the only product that I'm aware of that, uses the step-up approach in terms or the split infusion. Sorry not the step-up dosing the split infusion.

190
00:35:08.559 --> 00:35:29.879
Bijal D. Shah: and in terms of why it improves the safety output. I think it's twofold right. When we look at the Pk we actually see expansion fairly similar expansion, despite the lower initial priming dose with using the tumor burden to guide that

191
00:35:29.879 --> 00:35:44.449
Bijal D. Shah: what we're avoiding is putting in a very, very high

dose of cells in patients with higher tumor burden, where we might expect more toxicity, as was observed on the Tysogen study in adult all.

192
00:35:44.719 --> 00:35:48.579
Bijal D. Shah: So I think that that novelty

193
00:35:48.939 --> 00:35:55.649
Bijal D. Shah: does inform again the innovation there. I'm sorry in that delivery does inform the safety in terms of the second dose.

194
00:35:55.899 --> 00:36:03.569
Bijal D. Shah: This is really interesting. So we do see, you know, that the the bk continues to show increasing. You know.

195
00:36:04.069 --> 00:36:11.859
Bijal D. Shah: car T cell levels with that second priming with the second infusion. But what's really fascinating is.

196
00:36:12.039 --> 00:36:24.529
Bijal D. Shah: I mean, again, keep in mind. I'm a scientist. So I get kind of geeked out by this. But you know, are we priming the the tumor environment and setting the stage for the second infusion to do its job essentially.

197
00:36:24.719 --> 00:36:41.799
Bijal D. Shah: And when we talk about the persistence, thinking about that persistence of the car is not just a function of Hey, we have a 4 Mbb. Not just the low affinity binder, which also we've shown, and experimentally that contributes to this. But now also that delivery system adding to that benefit. It's

198
00:36:41.859 --> 00:36:53.249
Bijal D. Shah: it's really, really cool. And you know, it goes in terms of the toxicity mitigation piece. It allows us to resolve any low-grade toxicity such as low-grade crs before we give the full dose.

199
00:36:53.249 --> 00:37:16.699
Bijal D. Shah: So now, patients, I think, are also in a state where, hey? We've suppressed the interleukin 6, or done what we need to to now get the full dose and appreciate that benefit. So I don't know if I answered your question as well as I wanted to. I hope I did, but I

think it is certainly for me in clinical practice. It's the only car t cell therapy approved with the split infusion approach, and again with this safety profile that I'm excited about.

200
00:37:17.730 --> 00:37:24.279
Adina Hersko: Thank you. You had mentioned that the Felix Trial is now published in the New England Journal of Medicine. Will you be providing that with Cms.

201
00:37:24.680 --> 00:37:25.800
Bijal D. Shah: Yes, absolutely.

202
00:37:26.550 --> 00:37:28.019
Adina Hersko: Okay. Thank you very much.

203
00:37:32.840 --> 00:37:34.670
Drew Kasper: Any other questions from Cms.

204
00:37:38.290 --> 00:37:43.419
Drew Kasper: There are no new questions in the QA. Or no new raised hands.

205
00:37:43.830 --> 00:37:47.239
Drew Kasper: There are no new questions in the new tech mailbox.

206
00:37:48.020 --> 00:37:49.180
Drew Kasper: All right.

207
00:37:49.790 --> 00:37:53.720
Drew Kasper: So with that thanks again for your presentation.

208
00:37:54.250 --> 00:38:01.459
Drew Kasper: we'll now hear from presenters for Indeltra. You may now unmute your phone and introduce yourself.

209
00:38:03.880 --> 00:38:09.489
Catherine Chan: Good morning. My name is Katherine Chan, and I'm the Us. Medical lead at Amgen for small cell lung cancer.

210

00:38:09.610 --> 00:38:25.019
Catherine Chan: Just a few disclaimers before we get started. I'm an employee of Amgen, and today I will discuss evidence from single arm trial with time based endpoints such as progression-free survival and overall survival with treatment effects that can be difficult to interpret in the absence of a comparator arm.

211
00:38:25.250 --> 00:38:41.679
Catherine Chan: I appreciate the opportunity to be here today to discuss why Mdeltra, a novel delta like Ligand, 3. Bispecific T-cell engager meets the substantial clinical improvement criteria, and should be granted ntap status for fiscal year, 2026. Next slide, please.

212
00:38:44.190 --> 00:39:10.300
Catherine Chan: Imdeltra is a bispecific t cell engager immunotherapy that directs the patient's own T cell to kill. Dll, 3. Expressing cancer cells on May 16, th 2024, Imdeltra received accelerated approval from the FDA for the treatment of adult extensive stage, small cell lung cancer patients with disease, progression on or after platinum-based chemotherapy, and the confirmatory trial has recently completed enrollment.

213
00:39:10.830 --> 00:39:24.970
Catherine Chan: Mdeltra is the 1st and only bispecific T cell engager that binds to both Dll 3 on cancer cells and CD 3 on a patient's own T cell leading to T cell mediated cancer cell Lysis. Next slide, please.

214
00:39:28.030 --> 00:39:45.119
Catherine Chan: small cell lung cancer is an aggressive and devastating disease with extremely poor prognosis and limited options. Nearly two-thirdrd of patients with small cell lung cancer are diagnosed with extensive stage small cell lung cancer with the median survival. Approximately 12 months following initial therapy

215
00:39:45.600 --> 00:40:00.329
Catherine Chan: disease progression occurs often, and over the past 2 decades small cell lung cancer has continued to have a high unmet need with only 7% survival rate at 5 years, which remains relatively unchanged over the years. Next slide, please.

216
00:40:02.840 --> 00:40:12.889
Catherine Chan: Unfortunately, extensive staged muscle lung cancer has a high recurrence rate after first-line platinum-based chemotherapy,

and most patients relapse within 6 to 12 months.

217
00:40:13.100 --> 00:40:25.719
Catherine Chan: Patients have limited treatment options after progressing from frontline therapies. There are only 2 other therapies, Topotecan and luponectadine approved for second line, and no therapy specifically approved for 3rd line, plus

218
00:40:26.160 --> 00:40:34.719
Catherine Chan: these charts show the real world survival for patients being treated with available second line plus therapies, including topotecan and lupineidine.

219
00:40:34.950 --> 00:40:45.970
Catherine Chan: In the second line setting survival ranges from 4.3 to 5.9 months, and outcomes are worse in the 3rd line, setting with survival ranging from 3.9 to 4.4 months.

220
00:40:46.670 --> 00:40:53.510
Catherine Chan: Approximately 70% of patients die or do not receive next line of therapy after second line treatment.

221
00:40:54.250 --> 00:41:03.970
Catherine Chan: Other second line therapy also have high rate of grade, 3 or higher neutropenia in their pivotal trials with topotecan at 78% and lubinectadine at 46%,

222
00:41:04.510 --> 00:41:10.779
Catherine Chan: there remains a significant and met need for new therapies with improved outcomes and tolerable safety profiles.

223
00:41:11.200 --> 00:41:12.409
Catherine Chan: Next slide, please.

224
00:41:13.870 --> 00:41:15.569
Catherine Chan: This slide summarizes.

225
00:41:15.850 --> 00:41:17.730
Catherine Chan: I'm sorry the slide before

226

00:41:21.370 --> 00:41:31.650
Catherine Chan: this slide summarizes the claims made in the nthap application that support. Why, Mdeltra represents a substantial clinical improvement for extensive stage small cell lung cancer patients

227
00:41:31.900 --> 00:41:52.270
Catherine Chan: in the interest of time, I will not go into details on all the claims here. But we'll focus on the clinical evidence demonstrating that Mdeltra is a novel treatment options that offers substantial clinical improvement through deep and durable responses for patients with extensive stage, small cell lung cancer relapsed on platinum-based chemotherapy. Next slide, please.

228
00:41:54.800 --> 00:42:08.240
Catherine Chan: Mdeltra's pivotal study, Delphi, 301 is the phase, 2 open-label, multicenter, multi-cohort clinical trial in 3rd line, plus extensive stage, small cell lung cancer that evaluated the safety and efficacy of Mdeltra

229
00:42:08.740 --> 00:42:20.369
Catherine Chan: patients included in the study had at least 2 lines of treatment prior to participating in the trial. As discussed earlier, this heavily pretreated population has poor prognosis on current therapy.

230
00:42:20.660 --> 00:42:27.940
Catherine Chan: The average age of the patient population was 64 years old, with 48% over 65 years old.

231
00:42:28.630 --> 00:42:38.370
Catherine Chan: About 33% of patients receive 3 or more lines of therapy, and 73% of patients receive par ndpd-l. 1 therapy next slide, please.

232
00:42:39.960 --> 00:43:03.319
Catherine Chan: In the Delphi 301 trial Mdeltra showed durable efficacy in patients with extensive stage small lung cancer. In all 3 parts of the trial patients received a step-up dose of Mdeltra, one milligram intravenously on day, one of cycle, one followed by either 10 milligrams or 100 milligrams on day 8 and day, 15 of cycle one and every 2 weeks thereafter until disease progression.

233

00:43:03.720 --> 00:43:10.759
Catherine Chan: Among the 99 patients that received 10 milligrams dose every 2 weeks. Overall response rate was 40%.

234
00:43:11.250 --> 00:43:26.109
Catherine Chan: The Median time to objective response was 1.4 months. And among those who responded to Mdeltra, the initial data cutoff, 68% of patients responded for 6 months or more and 40% of patients were still responding. At one year.

235
00:43:26.400 --> 00:43:35.169
Catherine Chan: The Median duration of response was 9.7 months, ranging from 2.7 to 20.7 plus months. Next slide, please.

236
00:43:37.010 --> 00:43:53.470
Catherine Chan: An extended follow-up analysis was performed on the Delphi 301 trial, which showed similar secondary endpoints as the primary analysis, the long-term follow-up data showed a medium overall survival of 15.2 months and medium progression-free survival of 4.3 months.

237
00:43:53.600 --> 00:44:01.649
Catherine Chan: 12 months. Progression-free survival was 24% and 18 months overall survival was 46%.

238
00:44:02.080 --> 00:44:08.329
Catherine Chan: Overall survival was similar, regardless of progression, freezer interval after 1st line platinum treatment.

239
00:44:08.760 --> 00:44:09.970
Catherine Chan: Next slide please.

240
00:44:12.350 --> 00:44:27.269
Catherine Chan: Extensive stage, small cell lung cancer is also characterized by metastasis and brain metastasis occur in 40 to 70% of patients. About 23% of patients in the pivotal Delphi, 301 study has stable treated brain metastasis at baseline

241
00:44:27.610 --> 00:44:41.920
Catherine Chan: in extensive stage, small cell lung cancer patients with stable brain metastasis pretreated with 2 or more para therapies. Mdeltra showed similar clinical outcomes as patients without brain

metastasis in a post hoc analysis of Delphi 301.

242
00:44:42.920 --> 00:44:52.080
Catherine Chan: For example, overall response rate in the subset of patients with stable treated brain metastasis was 52%, and those without brain metastasis was 38%

243
00:44:52.390 --> 00:44:53.679
Catherine Chan: next slide, please.

244
00:44:55.080 --> 00:45:13.660
Catherine Chan: Importantly, indeltra also demonstrated a manageable safety profile with a low rate of discontinuation due to treatment-related adverse events. The most common adverse events in patients were cytokine, release, syndrome, fatigue, pyrexia, dysgousia, decreased appetite, musculoskeletal, pain.

245
00:45:13.660 --> 00:45:14.980
Catherine Bernstein: 3 min remaining.

246
00:45:15.870 --> 00:45:31.909
Catherine Chan: The most common treatment-related events were Cytokine release syndrome, which primarily occurred in cycle. One was mostly grade, one to 2, and was generally manageable with supportive care. Grade 3 or higher neutropenia occurred at 6%

247
00:45:32.870 --> 00:45:41.220
Catherine Chan: overall. Mdultra demonstrated a manageable safety profile with a low rate of discontinuation due to treatment-related adverse events.

248
00:45:41.420 --> 00:46:00.669
Catherine Chan: Mdeltra also demonstrated a similar safety profile in patients with stable treated brain metastasis specifically for neurotoxicities, including immune effector cell-associated neurotoxicity, the post hoc analysis found similar safety data between patients with and without stable brain metastasis.

249
00:46:01.490 --> 00:46:02.790
Catherine Chan: Next slide, please.

250

00:46:04.310 --> 00:46:32.749
Catherine Chan: In conclusion, there is a profound need in extensive stage. Small cell lung cancers who suffer from devastating outcomes in suboptimal care. On previously available therapies. Indeltra is the only approved Dll. 3 directed CD. 3 T. Cell engager for the treatment of extensive stage small cell lung cancer, and it offers substantial clinical improvement through deep and durable response for patients with extensive stage small cell lung cancer relapsed on platinum-based chemotherapy.

251
00:46:32.860 --> 00:46:44.800
Catherine Chan: As mentioned previously, the phase 3 confirmatory trial has completed enrollment, and we look forward to sharing results when they're available. Thank you for your consideration of our application. I would be happy to answer any questions.

252
00:46:49.570 --> 00:46:52.320
Drew Kasper: Thank you very much for your presentation.

253
00:46:53.030 --> 00:46:55.680
Drew Kasper: Are there any questions from the public?

254
00:47:05.142 --> 00:47:12.420
Drew Kasper: I do not have any questions in the QA. At this time attendees.

255
00:47:13.260 --> 00:47:17.850
Drew Kasper: There are no raised hands from the attendees.

256
00:47:20.050 --> 00:47:23.479
Drew Kasper: and we don't have any questions in the new tech mailbox.

257
00:47:25.570 --> 00:47:41.739
Drew Kasper: I'm gonna call for questions from Cms next. But if the public happens to have a question during the Cms. Time, I we wouldn't we wouldn't exclude it when we, when we move on from the public questions onto Cms. If you have a question from the public

258
00:47:42.248 --> 00:47:50.520
Drew Kasper: feel free to still raise your hand or type it into the QA. But we will at this time move on to questions from Cms.

259
00:47:54.460 --> 00:47:59.500
Drew Kasper: So Dr. Belisa, please go ahead and unmute.

260
00:48:02.030 --> 00:48:02.880
Wally Belleza: Good morning.

261
00:48:03.380 --> 00:48:29.549
Wally Belleza: Thank you for your presentation. I have an issue with my video here. If no parallel studies have been conducted with other treatment agents. How did you control for the potential differences in patient demographics, the prior treatments that they had, and other factors when comparing Mdeltra the results of the Mdeltra studies to studies, assessing other relevant therapies.

262
00:48:32.670 --> 00:48:39.629
Catherine Chan: Yeah, that's a great question, I think, you know. Given the nature of this disease, Indultra was 1st studied in a multicohort study

263
00:48:39.970 --> 00:48:49.050
Catherine Chan: approved by FDA under accelerator approval based on the overall response rate and duration of response in in light of the significant and met need for this patient.

264
00:48:49.060 --> 00:49:18.330
Catherine Chan: I believe, like when the results of Delphi 301 are looked at holistically, including the overall response rate, duration of response, overall survival, and Pfs. With the caution that we have included, and Deltra is still a substantial clinical improvement for extensive stage small cell lung cancer who have failed 2 or more therapies. The patient population has extremely poor outcomes with real world evidence showing mean overall survival of 4 to 5 months in patients receiving 3rd line systemic therapy.

265
00:49:18.380 --> 00:49:43.670
Catherine Chan: Other therapies have median overall duration of response of 3.3 months to 5.3 months. So when patients are so sick that the duration of response is measured in months. The Median duration of response of Indeltra of 9.7 months is a substantial clinical improvement. So when this is considered along with other outcomes that have been studied. It is clear that ntap does meet the ntap criteria.

266
00:49:46.070 --> 00:49:46.770
Wally Belleza: Thank you.

267
00:49:46.900 --> 00:49:48.330
Wally Belleza: No other questions here.

268
00:49:51.910 --> 00:50:00.179
Adina Hersko: Hi, thank you for your presentation when you're looking at the overall response rates. Did you provide a comparison to other therapies?

269
00:50:02.560 --> 00:50:16.960
Catherine Chan: Yes, in the application we have kind of outlined some of the, you know, other kind of background information, including other therapies, you know, with the overall response rate. As you know, you know, it is not kind of head to head kind of comparison.

270
00:50:17.760 --> 00:50:31.420
Adina Hersko: So when we're looking at the studies and trying to look at those numbers, how can we determine, based on what you're providing? So what Dr. Belize is asking is, how did you match those patients to determine that those can be compared.

271
00:50:32.930 --> 00:51:02.609
Catherine Chan: Yeah, while we understand, kind of head-to-head is not a requirement. But, like, I think, as I mentioned, kind of in the previous kind of answer. I think holistically, because of all the data that we've provided, including, you know, overall response rate, duration of response, overall survival and Pfs, and giving kind of that background of other therapies, you know, with real world evidence really showing that overall survival of 4 to 5 months

272
00:51:02.680 --> 00:51:13.549
Catherine Chan: and given kind of some of the limited available options for therapy. We strongly believe that the duration of response of Mdeltra of

273
00:51:14.630 --> 00:51:38.910
Catherine Chan: substantial kind of clinical improvement, we will have an indirect kind of comparison that is underway to evaluate the relative benefit and survival outcomes and response between Abdeltra versus other therapy of choice. While this is not yet published. We

expect them to be available in March 2025, and we'll provide them as an update to this application.

274
00:51:39.570 --> 00:51:40.370
Adina Hersko: Thank you.

275
00:51:49.930 --> 00:51:52.820
Drew Kasper: Are there any further questions from Cms

276
00:51:54.330 --> 00:51:57.860
Drew Kasper: or attendees? Questions from Cms. Go ahead and unmute.

277
00:52:00.050 --> 00:52:03.830
Drew Kasper: Do not have any new questions in the Q. And a. From the public.

278
00:52:05.130 --> 00:52:07.769
Drew Kasper: I don't have any raised hands from attendees.

279
00:52:11.390 --> 00:52:14.399
Drew Kasper: and I do not have any

280
00:52:16.786 --> 00:52:24.879
Drew Kasper: questions that have come into the new tech mailbox. So with that thanks again for your presentation.

281
00:52:26.480 --> 00:52:27.340
Catherine Chan: Thank you very much.

282
00:52:28.730 --> 00:52:36.410
Drew Kasper: And we will now hear from presenters for duragraphs. You may now unmute your phone or

283
00:52:37.080 --> 00:52:41.299
Drew Kasper: Catherine. I think you should be all set and introduce yourselves. Thank you.

284
00:52:42.600 --> 00:52:56.380
Steven S. Brooks: Thank you. Hello! I'm Steve Brooks. I'll speak today

about merozymes duragraft a solution for the preservation of vascular conduits during coronary artery bypass surgery. My disclosures are that I was a former employee and stockholder. Next slide.

285
00:52:56.520 --> 00:53:17.249
Steven S. Brooks: There are over 400,000 coronary artery bypass surgeries in the United States every year. Multiple studies have documented cabbage's clinical value, and it has a class one indication. The latest Acc. Aha, guidelines. Studies have shown that cabbage surgery improves survival and symptoms in patients with advanced and complex coronary artery disease next slide, please.

286
00:53:17.250 --> 00:53:30.330
Steven S. Brooks: Unfortunately, over the past 60 years there's been little innovation to address the major issue of vein, graft, failure, vein, graft, disease progressing to vein graft failure remains the major cause of long-term failure in bypass surgery. Next slide, please.

287
00:53:30.520 --> 00:53:53.729
Steven S. Brooks: 85% of surgeries employ veins as conduits. This slide shows the findings of meta-analysis. Looking at vein graft, failure rates at different time points, the failure rate of individual grafts. The graft level failure rate is approximately 30% in the 1st year, increasing to more than 40% between 5 and 10 years. Most patients have more than one vein graft. The patient level

288
00:53:53.810 --> 00:54:11.510
Steven S. Brooks: graft failure rate is 50% at one year. Multivariate analysis from the prevent 4 trial looked at causative factors for vein graft failure. One of the most important was the vein graft storage solution used with a p-value of P less than 0 point 0 0 1 next slide, please.

289
00:54:11.860 --> 00:54:35.659
Steven S. Brooks: This slide depicts the pathophysiology of vein, graft, disease, cabbage grafts, experience, stress resulting from the physical trauma of harvesting and handling post-harvest ischemia, oxidative stress and reperfusion, injury. The occurrence of vein graft, disease, post cabbage can be divided into 3 temporally distinct, but pathophysiologically related mechanisms thrombosis which occurs hours to less than a month.

290
00:54:35.670 --> 00:54:57.530

Steven S. Brooks: Intimal hyperplasia, which occurs within months and atherosclerosis, which occurs at more than 12 months. This process begins with the accumulation of platelets, inflammatory cells, and thrombi. It triggers smooth muscle, cell proliferation which manifests as wall thickening. This progresses to atheroma formation. This damage to the vein graft endothelium which

291
00:54:57.760 --> 00:55:10.910
Steven S. Brooks: compromises the structural and functional integrity of the graphs is identified as the main trigger for these pathologic processes within the conduit and is the target of engraft preservation with durograph next slide, please.

292
00:55:11.000 --> 00:55:30.799
Steven S. Brooks: These are the important clinical impacts of vein, graft, disease and vein graft, failure, vein, graft, failure can lead to myocardial infarction, repeat revascularization, hospital readmission, which in and of itself is an important cause of morbidity and mortality, as well as a great cost to the healthcare system and poor quality of life. Next slide, please

293
00:55:30.900 --> 00:55:57.069
Steven S. Brooks: to target this problem. Marizyme has developed duragraft, a de novo cleared and cemarked solution for the flushing and storage of vascular conduits used during the harvesting and grafting interval bypass surgeries. This is the only vein graft, preservation, and flushing solution which is FDA cleared or ce marked for this indication for use. All others are used off label and not designed for purpose. Duragraft is prepared by pouring the 2 containers

294
00:55:57.070 --> 00:56:20.010
Steven S. Brooks: into a bowl during preparation for the surgery. This is similar to how saline or buffered saline would be poured into the same bowl. The surgeon harvests the conduits, flushes, duragraph down the conduit, and then stores the conduit in the bowl until it is ready to be sewn into the patient. The preparation and use of duragraph, therefore, does not disrupt or modify the natural course of the surgical procedure.

295
00:56:20.090 --> 00:56:44.859
Steven S. Brooks: Durrograft itself is composed of inorganic salts and organic components. All components are normal constituents of blood, and are included for their roles in maintaining the extracellular environment of vascular conduits together. The components impart ph

balance and buffering ionic balance and isotonicity and a reducing environment to reduce or prevent the risk of oxidative damage during ischemic storage. Next slide, please

296
00:56:45.140 --> 00:57:09.719
Steven S. Brooks: multiple preclinical studies, including the 3 summarized here and included on the product's FDA label demonstrate the pathophysiology of Durgraff's effects on the veins. This includes the reduction of oxidative damage and stress decreased hypoxic damage and increased antioxidant reserves, and, most importantly, the maintenance of the structural and functional integrity of the Vascular endothelium. Next slide please.

297
00:57:09.930 --> 00:57:39.759
Steven S. Brooks: 5 clinical studies demonstrate the pathophysiology of duragraft's use and important clinical outcomes. The 1st is a randomized, controlled trial of 125 patients, undergoing first-time bypass surgery. It was conducted at 7 sites in Canada and Europe between 2014 and 16, and employed in intra-patient randomization, where each patient had at least one duragraft treated vein, graft, and one Saline treated vein graft patients were followed for a year and underwent Ct. Scans at 1, 3, and 12 months. Next slide, please.

298
00:57:39.910 --> 00:57:54.400
Steven S. Brooks: The outcomes are seen here at 3 months there were no mace events. At 12 months there was no death or repeat revascularization in either arm. One vein graft had an occlusion, and a myocardial infarction was seen in that patient in a saline treated graft.

299
00:57:54.510 --> 00:58:08.290
Steven S. Brooks: Ct. Analysis revealed that at 12 months duragraph treated veins had a smaller mean wall thickness versus their saline treated control at 0 point 1 2 compared to 0 point 2 with a p of 0 point 0 2.

300
00:58:08.290 --> 00:58:28.009
Steven S. Brooks: The change in maximum focal narrowing between one and 12 months in the whole graft was 0 point 2 versus 4.7 this study demonstrates the Pathophysiology of vein, graft, disease, vein, wall thickening, which then progresses to stenosis and occlusion, and Durrograft suppress the cystology. Next slide, please.

301
00:58:28.010 --> 00:58:54.950

Steven S. Brooks: The second study is the European durograph registry. This was a European cemark, post-approval study. It was a real world single arm study, with 45 sites in 8 European countries that enrolled 2,964 patients who received duragraph during bypass surgery, 2,522 patients had isolated cabbage. The outcomes are depicted here with low rates of major adverse cardiac events, cardiovascular death. Mi, and repeat revascularization. Next slide.

302
00:58:55.080 --> 00:59:06.769
Steven S. Brooks: In order to place this single arm study into context, we worked in conjunction with the staff of the Sts. Registry, to perform a propensity match between the durograph registry and the Sts. Registry.

303
00:59:06.770 --> 00:59:26.339
Steven S. Brooks: The Sts. Registry contains data from 98% of us bypass patients. The primary propensity match model matched 35 variables associated with clinical outcomes in cabbage surgery. The primary outcome measure was survival which was determined for matching the Sts patients to the Us. National death Index. Next slide, please.

304
00:59:26.870 --> 00:59:50.509
Steven S. Brooks: 2,400 of the 2522 patients in the Duragraft Registry were matched to 2,400 of 294,000 patients in the Sts. Registry. From the same period of time a mortality benefit is seen here out to 3 years, with the curve separating at 8 months in favor of duragraft. The log rank p-value was 0 point 0 1 6 over this time period demonstrating a long-term mortality.

305
00:59:50.510 --> 00:59:50.860
Catherine Bernstein: I would be.

306
00:59:50.860 --> 00:59:52.510
Steven S. Brooks: Benefit. Thank you.

307
00:59:52.720 --> 00:59:59.699
Steven S. Brooks: Of 7.3 7% versus 9.6 5% at 3 years in favor of duragraph. Next slide, please.

308
01:00:00.320 --> 01:00:23.800
Steven S. Brooks: The 3rd study was a retrospective cohort study performed at the Va. Medical Center in Boston. Comparing the performance of Gala, the direct precursor of duragraft to saline,

sorry gala and duragraft have identical components differing only in their manufacturing and shelf life patients were enrolled who underwent 1st time bypass the control group of 1,400 patients had standard of care treatment with saline.

309
01:00:23.800 --> 01:00:47.379
Steven S. Brooks: Between 1996 and 1999, the treatment group of 1,036 patients had their vein grafts treated with duragraft between 2,001 and 2,004. The results demonstrated benefit of duragraft at 1,000 day follow-up with a 45% reduction in myocardial infarction, 35% reduction in repeat revascularization and 19% reduction in major adverse events. Next slide, please.

310
01:00:48.010 --> 01:00:56.769
Steven S. Brooks: The final study was performed after an observation by a physician that patients in whom he had used duragraft had lower elevations of troponin. Post-OP

311
01:00:56.980 --> 01:01:08.650
Steven S. Brooks: troponin is a biomarker indicating myocardial cell death, and is used to detect post-OP mi. In addition to flushing and storing the grafts with duragraft, the surgeon would flush durograft down the graft and into the vascular bed

312
01:01:08.870 --> 01:01:31.940
Steven S. Brooks: patients were studied who underwent cabbage between 2019 and 20, using either durograft or a combination of saline and bisecco. Bisecco is a commercially available human plasma derivative, indicated for intravascular volume, expansion and protein replacement mixed with saline has also been used as a graft storage solution during bypass surgery to bring the ph solution to physiologic levels. Next slide. Please

313
01:01:33.330 --> 01:01:35.149
Steven S. Brooks: advance one more, please.

314
01:01:35.780 --> 01:01:51.020
Steven S. Brooks: 272 patients were identified who underwent bypass surgery. During this interval they were divided into 2 propensity match groups of 83 patients each, which are well matched. You can see in the plot to the right, like differences in troponent eye levels, for the saline separated early.

315

01:01:51.060 --> 01:02:13.120
Steven S. Brooks: Thank you with statistically significant decreases in favor of durograph. Starting at 3 to 6 h post-OP, and continuing at one to 4 days post-OP. The maximum troponin eye level also was significantly decreased. The authors concluded that vein storage and repeated flushing of the distal anastomosa for duragraft was associated with a significantly lower troponin levels. Post-surgery

316
01:02:13.120 --> 01:02:40.439
Steven S. Brooks: suggesting enhanced myocardial protection when compared to saline bisecco next slide please in conclusion. Duragraft is a solution for the preservation of vascular conduits during bypass surgery which targets the Pathophysiology of vein, graft, disease and vein graft failure by preventing damage to the endothelium. Multiple clinical studies validate the mechanism of action and pathophysiology. With 4,315 patients studied to date, and over 13,000 patients treated commercially.

317
01:02:40.580 --> 01:02:51.040
Steven S. Brooks: the multiple, large and small clinical trials all demonstrated positive results, results confirming the pathophysiology and correlating with positive clinical outcomes. Thank you very much.

318
01:02:54.520 --> 01:02:58.940
Drew Kasper: Thank you very much for your presentation, and with that

319
01:02:59.610 --> 01:03:03.359
Drew Kasper: we'll now open up for questions from the public

320
01:03:06.580 --> 01:03:09.059
Drew Kasper: which may include other applicants as well.

321
01:03:12.400 --> 01:03:16.540
Drew Kasper: We don't have any questions in the Q. And A. At this time.

322
01:03:17.560 --> 01:03:18.300
Steven S. Brooks: Okay.

323
01:03:18.720 --> 01:03:21.850
Drew Kasper: We don't have any hands up from attendees.

324
01:03:26.640 --> 01:03:40.829
Drew Kasper: Don't have any new questions in the new tech mailbox. So with that again, if you're with the public. Feel free to ask the questions as we move on here to Cms. Questions.

325
01:03:41.010 --> 01:03:46.600
Drew Kasper: Folks from Cms can now go ahead and unmute and ask your questions. Thanks.

326
01:03:47.450 --> 01:03:50.560
Sophia Chan: Good morning, Dr. Brooks. This is Sophia Chan, Cms.

327
01:03:51.234 --> 01:04:05.390
Sophia Chan: You discussed the result on 36 month, all cost mortality. Do you have any results that are cardiac specific, and can be directly attributed to duragraph.

328
01:04:05.790 --> 01:04:31.759
Steven S. Brooks: Yeah, that's a great question. So the only we work very closely with the Sds registry themselves, and the hardest data that we could come up with was mortality. When we started looking at myocardial infarction, the problem is this is data collected from all across the United States, 98% of patients that have bypass surgery, and these sites use different definitions of myocardial infarction.

329
01:04:31.760 --> 01:04:54.529
Steven S. Brooks: repeat revascularization isn't always captured. So the only hard data that we could really measure was mortality. We really worked hard with them to figure out what other data we could really put strong confidence in. And unfortunately, that's a limitation of the study method, comparing a single arm study with an existing registry.

330
01:04:55.430 --> 01:05:20.089
Sophia Chan: I see. And have you considered other post-operative risk factors that might also have impact on the outcomes? I'm thinking about post-operative factors like treatment. Protocols, Medication. Use down the line or medication, assist adherence or additional procedures, health status, etc.

331
01:05:20.370 --> 01:05:34.330
Steven S. Brooks: Yeah, so you bring up a great point. And these are

all important factors in outcomes and revascularization. So 30 day mortality is very highly correlated with operative procedure and operative risk factors.

332
01:05:34.400 --> 01:05:57.719
Steven S. Brooks: And a lot of the things that you're also describing. Medication treatment control of hypertension control of other risk factors are absolutely related to that when we did the propensity match. So for starters our durrgraph registry, we follow these patients out. For years. We did capture. We had 5 year follow up on many of our patients, and we captured all these things, repeat

333
01:05:57.720 --> 01:06:08.720
Steven S. Brooks: hospitalizations, the medications that we were on, and they were all receiving standard of care to a high degree. When we work with the Sts registry and we made our propensity match.

334
01:06:08.720 --> 01:06:23.660
Steven S. Brooks: we use 35 different variables, and these were drawn from the literature, and highly correlated with both acute surgical mortality, intermediate and long term, and I can read the list. I have it in front of me, but it includes

335
01:06:23.690 --> 01:06:49.129
Steven S. Brooks: demographic, such as age, sex, race, smoking, lung disease, cardiac risk factors, pre-OP cardiac status, such as pulmonary hypertension, unstable angina, history of congestive failure, heart failure, pre-OP cardiac status issues. We looked at coronary anatomy. Was it left main? 3 vessel disease? We looked at intraoperative factors. These were all part of our

336
01:06:49.130 --> 01:06:56.579
Steven S. Brooks: propensity. Score variables, including were the veins harvested endovascularly.

337
01:06:56.580 --> 01:07:13.160
Steven S. Brooks: How many distal anastomosis was their lemograft used! How many arterial grafts were used! How many grafts total. So we did try. And you know, 35 variables really have a comprehensive list of both early stage and long-term outcome variables.

338
01:07:14.160 --> 01:07:23.850
Sophia Chan: I see. Can you help us understand why Durograp has an

important significant impact at a 36 month time point.

339
01:07:24.050 --> 01:07:29.029
Sophia Chan: but not at a 12 month or 24th month, post cabbage.

340
01:07:29.030 --> 01:07:34.630
Steven S. Brooks: Yeah. I wonder if you can go back to the slide? I'll tell you which number

341
01:07:34.820 --> 01:07:36.380
Steven S. Brooks: slide number 5.

342
01:07:37.060 --> 01:08:04.569
Steven S. Brooks: It's the one showing the Pathophysiology. So you know, it's interesting. One of the main mechanisms of actions in the Pathophysiology here is protecting the endothelium and the way that vein graft progresses is really starts beyond a month. It's in the second stage where smooth muscle cells start to proliferate. And so when we've done a lot of preclinical studies that have shown preservation of

343
01:08:04.570 --> 01:08:13.330
Steven S. Brooks: of the vascular endothelium. And this process is really slow. One of the interesting things with our randomized trial we had originally designed it for 3 months.

344
01:08:13.330 --> 01:08:26.240
Steven S. Brooks: and we saw that at 3 months, and these were patients who were internally randomized. So each patient had a duragraph treated vein and a saline treated vein, and the progression in both

345
01:08:26.240 --> 01:08:50.719
Steven S. Brooks: was so slow that we had to extend the study to a year. So really, this is a slow process. So it makes sense that as it accelerates beyond smooth muscle, cell proliferation and into atherosclerosis development, that this is a slow process that occurs over years, and it was interesting that, you know by protecting it early on, we've slowed or delayed this process and our Pathophysiology

346
01:08:50.750 --> 01:09:04.729
Steven S. Brooks: with the randomized trial, using Ct. Correlated. Then with these outcome studies which showed later studies, later

outcomes of mortality. Interestingly, also, our

347
01:09:04.740 --> 01:09:23.279
Steven S. Brooks: BA study, we were able to measure these patients. We followed them. We had follow up out to an average 8 years, and we were able to see myocardial infarction repeat revascularization and death, and we showed positive benefits in in those important outcomes, as well.

348
01:09:24.260 --> 01:09:30.689
Sophia Chan: I see and I also want to go back to slide number 36.

349
01:09:33.783 --> 01:09:39.590
Sophia Chan: Yes, this one in the yes, in them

350
01:09:39.990 --> 01:09:47.269
Sophia Chan: bullet in the middle. It's it talks about result observed within 15 min. Post.

351
01:09:47.279 --> 01:09:47.699
Steven S. Brooks: Yeah.

352
01:09:47.700 --> 01:09:56.309
Sophia Chan: And storage. I'm wondering. In the same paper by Hujak and team.

353
01:09:56.550 --> 01:10:02.570
Sophia Chan: There seemed to be no significant difference between the treatment and the control group

354
01:10:03.380 --> 01:10:13.079
Sophia Chan: 30 min, and and later on, so how? How did the 15 min result came about? Come about.

355
01:10:14.360 --> 01:10:16.960
Steven S. Brooks: Catherine, are you on the phone? Are you on the

356
01:10:22.210 --> 01:10:23.759
Steven S. Brooks: Okay, Kathy patch?

357
01:10:23.760 --> 01:10:31.970
Drew Kasper: Catherine, are you able to are you able to speak, Catherine? I know you had some audio issues. We thought we had that resolved.

358
01:10:36.052 --> 01:10:39.367
Steven S. Brooks: Okay, I guess not. So

359
01:10:39.940 --> 01:10:56.410
Steven S. Brooks: this was, I'm sorry I'm not able to answer this question at this time, but we can absolutely get back to you on this. This was a study where we we isolated pig, mammary veins and

360
01:10:56.410 --> 01:11:10.950
Steven S. Brooks: and in perfusion treated them with either duragraft or saline, and we were able to stain them for looking at damage to the vascular endothelium. We saw.

361
01:11:11.010 --> 01:11:35.219
Steven S. Brooks: you know, after prolonged exposure, that vascular endothelium was preserved longer in the duragraft, treated veins versus arteries compared to the saline. But I apologize, but we can absolutely get you that more answers to this study offline.

362
01:11:35.740 --> 01:11:36.380
Sophia Chan: Sure.

363
01:11:36.760 --> 01:11:39.760
Sophia Chan: Thank you. No further questions for me.

364
01:11:43.400 --> 01:11:51.749
Drew Kasper: Yeah. And I think I think Catherine can can see us through her zoom connection. But I don't see her phone

365
01:11:52.060 --> 01:11:55.360
Drew Kasper: line that we had unmuted anymore.

366
01:11:55.360 --> 01:12:01.936
Drew Kasper: She's speaking, but it's not coming, it's not the audio is not coming on. I don't know. I apologize.

367
01:12:02.250 --> 01:12:05.779
Drew Kasper: you know I apologize as well. Yeah, I don't know what happened.

368
01:12:06.170 --> 01:12:25.470
Drew Kasper: but it looks like we lost that phone line. Now shoot well, remember, we also yeah, have the ability to accept comments so you could submit any written comments following the Town Hall up to that deadline there. With any information that that you'd like to add. So thanks.

369
01:12:26.310 --> 01:12:29.990
Drew Kasper: Okay, any other questions from Cms or from the.

370
01:12:29.990 --> 01:12:44.800
Adina Hersko: One thing I wanted to clarify I thought I had heard at 1 point I just wanted to clarify. Did you mention? I think it was on the next slide after this one that in the you did a study and the vein storage solution was the biggest factor in vein graft failure. Just wanted to clarify.

371
01:12:44.800 --> 01:12:53.550
Steven S. Brooks: So that was actually from the prevent for study. So that was a very large study of several 1,000 prospective bypass

372
01:12:53.550 --> 01:13:16.740
Steven S. Brooks: patients who were receiving experimental treatment. When they controlled. They published a subsequent paper on the Prevent for Data, where they looked at the types of vein graft, storage solutions that patients had received and predominantly saline. But there also was buffered saline, and there was also patients blood.

373
01:13:16.740 --> 01:13:36.520
Steven S. Brooks: Let's use the storage solution, and the buffered saline had a very strong, statistically significant correlation with the outcomes of repeat revascularization and the p-value for that correlation was less than 0 point 0 0 1.

374
01:13:39.170 --> 01:13:44.129
Adina Hersko: Got it. So it was just a study looking at those 3, and determining how they affected.

375
01:13:44.680 --> 01:13:52.680
Steven S. Brooks: That wasn't the primary purpose of the study. This was a sub-analysis that they did. They published multiple studies coming off of the

376
01:13:52.820 --> 01:14:07.500
Steven S. Brooks: that I can give you the reference, and that was from the prevent 4 trial. This was, it's on the slide at the bottom. It's it's the second one hars camp et Al. In Jama in 2014.

377
01:14:09.300 --> 01:14:11.450
Adina Hersko: Thank you. Appreciate the clarification.

378
01:14:11.750 --> 01:14:12.330
Steven S. Brooks: Yeah.

379
01:14:16.804 --> 01:14:26.379
Steven S. Brooks: I'm I got a text from Miss Davis. Let Kathy Patrick may be able to speak now to address address the previous question, Kathy, are you on?

380
01:14:34.310 --> 01:14:35.100
Steven S. Brooks: Okay?

381
01:14:35.720 --> 01:14:36.900
Steven S. Brooks: Maybe not.

382
01:14:38.710 --> 01:14:39.810
Steven S. Brooks: Okay. Sorry.

383
01:14:41.640 --> 01:14:49.230
Drew Kasper: It does look like she would be connected with audio through computer now, and unmuted.

384
01:14:50.010 --> 01:14:57.209
Steven S. Brooks: Says she. She texted that she's speaking sorry. I apologize for having technical difficulties on our side. So.

385

01:14:57.370 --> 01:15:02.980
Drew Kasper: Oh, technology is great when it works. But we all know it doesn't always break absolutely.

386
01:15:04.343 --> 01:15:12.419
Drew Kasper: Yeah, we can still default to the you know the ability to submit written comments. Post town hall.

387
01:15:12.660 --> 01:15:13.939
Steven S. Brooks: Okay, go ahead.

388
01:15:15.680 --> 01:15:18.750
Drew Kasper: Any other questions from Cms or the public.

389
01:15:23.400 --> 01:15:26.140
Drew Kasper: There are no open questions in the Q. And A.

390
01:15:26.260 --> 01:15:28.559
Drew Kasper: There are no raised hands from attendees.

391
01:15:30.020 --> 01:15:38.160
Drew Kasper: and there are no new questions in the new tech mailbox and.

392
01:15:38.160 --> 01:15:42.200
Steven S. Brooks: I I just got one more note let Kathy's mic may be working now.

393
01:15:43.388 --> 01:15:48.159
Drew Kasper: Let's give it one more try, Kathy, are you able to join? audio?

394
01:15:48.450 --> 01:15:49.300
Drew Kasper: Mike?

395
01:15:55.220 --> 01:15:57.170
Drew Kasper: Okay, nice.

396
01:15:57.920 --> 01:16:00.150

Steven S. Brooks: No, I guess not. Okay. Sorry.

397
01:16:03.553 --> 01:16:07.900
Drew Kasper: It's alright. Alright, and last, call for questions.

398
01:16:10.100 --> 01:16:15.050
Drew Kasper: Okay, well, with that we'll move on to our 1st break.

399
01:16:15.870 --> 01:16:19.929
Drew Kasper: and we'll meet back here in 10 min.

400
01:16:20.050 --> 01:16:23.439
Drew Kasper: Thanks again. Everyone see you at 1030,

401
01:16:26.970 --> 01:16:30.830
Drew Kasper: and we'll be starting back up momentarily here.

402
01:16:30.940 --> 01:16:36.339
Drew Kasper: Just wanted to provide some reminders here

403
01:16:36.600 --> 01:16:39.360
Drew Kasper: or for those that may have recently joined.

404
01:16:40.150 --> 01:17:03.130
Drew Kasper: Attendees may submit their questions, using the Q&A feature at the bottom of the screen, or you can use the raise hand feature in zoom, and we will enable you to unmute and ask your question verbally. Those who are dialed in by telephone only. You'd need to email your questions to the Cms new tech email box at New T. ech@cms.hhs.gov.

405
01:17:04.600 --> 01:17:19.640
Drew Kasper: I'd like to remind all the presenters that we have allotted exactly 10 min for each presentation, after which we'll have questions from the public and then from Cms. With responses from presenters. Cms. Will advance the slides for each presentation, and presenters should indicate when to advance to the next slide.

406
01:17:20.660 --> 01:17:31.310
Drew Kasper: and with that we have hit 1030, so we will now hear from

presenters for a cellular tissue, engineered vessel tide, or Atv.

407
01:17:31.930 --> 01:17:35.499
Drew Kasper: You may now unmute and introduce yourself. Thanks.

408
01:17:35.900 --> 01:17:49.060
Laura Niklason: Thank you very much. My name is Laura Nicholson. I'm the founder and the CEO of Humacyte, and have been involved in the development of the acellular tissue engineered vessel, or Atev. From the beginning. Next slide, please.

409
01:17:51.390 --> 01:18:04.560
Laura Niklason: The Atav is a 1st of its kind, bioengineered, implantable blood vessel, and it's anticipated to be indicated for use in adults as a vascular conduit for arterial injury. Repair

410
01:18:04.790 --> 01:18:09.199
Laura Niklason: when autologous vein is not feasible as a repair conduit.

411
01:18:09.790 --> 01:18:21.470
Laura Niklason: we believe that atav meets the substantial clinical improvement. Criterion set out by by the ntap, including being associated with lower conduit infection rates.

412
01:18:21.620 --> 01:18:39.940
Laura Niklason: lower amputation rates significantly improved. Secondary patency rates. In addition, even compared to autologous vein, which is the gold standard, the atav enables quicker reperfusion because it's available off the shelf and does not require harvest time. Unlike autologous vein, next slide.

413
01:18:41.990 --> 01:18:48.859
Laura Niklason: so Atav is truly a breakthrough in regenerative medicine. It's an engineered human blood vessel that's available off the shelf.

414
01:18:49.150 --> 01:19:01.699
Laura Niklason: It's universally implantable. In fact, we've treated nearly 600 patients with the Atef over more than 12 years, and with over 1,200 patient years of exposure. We've never had an instance of rejection.

415
01:19:01.990 --> 01:19:09.909
Laura Niklason: Importantly, the atav also repopulates with cells from the patient after it's implanted, and we believe this confers durability and also

416
01:19:10.720 --> 01:19:12.620
Laura Niklason: infection. Next slide.

417
01:19:14.810 --> 01:19:28.370
Laura Niklason: Very briefly, the way the Atav is manufactured is from human cells that are seeded onto a degradable polymer scaffold. That's 40 cm long and 6 in diameter, and that's the dimensions of the atav

418
01:19:28.480 --> 01:19:37.089
Laura Niklason: the cells attach. And then they grow for 2 months, and while they're growing they secrete extracellular matrix, and the polymer scaffold dissolves.

419
01:19:37.350 --> 01:19:54.320
Laura Niklason: After 2 months in a final step we wash the cells out of the tissue. So the final atav is bioengineered human extracellular matrix that's mechanically very strong, and it has a shelf life of 18 months when stored at refrigerated conditions. Next slide

420
01:19:56.770 --> 01:20:18.220
Laura Niklason: for the treatment of vascular trauma. It's important to look sort of at the causes of trauma and different aspects of that in the civilian and medicare populations. Vascular trauma is defined as an injury to an artery or vein, and we're focused on the limbs here. Vascular trauma can be due to either penetrating or blunt injury.

421
01:20:18.310 --> 01:20:34.249
Laura Niklason: and it typically interrupts. Blood flow to distal tissues, organs, and limbs. Causes of vascular trauma, particularly in the Medicare population, can include falls. Motor vehicle accidents, industrial accidents, but can also include violence-related injuries. Next slide.

422
01:20:36.690 --> 01:21:06.290
Laura Niklason: If we look at the methods for treatment of vascular

trauma, they're actually pretty limited. Right now, a patient comes to the emergency room, and several hours later arrives in the operating room. At that time the surgeon has one of 3 options. He or she can either spend another hour, harvesting vein from the patient to repair the artery which injures the patient further. But many medicare patients, particularly those who've had prior vein harvest, or who have varicosities are not suitable for this procedure.

423
01:21:06.340 --> 01:21:16.730
Laura Niklason: In that case the surgeon has to fall back to synthetic grafts made out of plastic or teflon, but those plastic grafts tend to do poorly when they're implanted into contaminated wounds.

424
01:21:17.150 --> 01:21:23.399
Laura Niklason: Failing that, the surgeon can ligate the artery and amputate the limb next slide

425
01:21:25.830 --> 01:21:33.420
Laura Niklason: we believe that the atav is a new treatment option, particularly for patients who lack available vein to repair their injured arteries.

426
01:21:33.880 --> 01:21:48.649
Laura Niklason: As I will show you in the subsequent slides we have, we have comparator data to historical benchmarks which show that the that the atav has better patency than synthetic grafts, a lower infection rate and results in improved limb. Salvage

427
01:21:48.880 --> 01:21:49.870
Laura Niklason: next slide.

428
01:21:52.820 --> 01:22:02.580
Laura Niklason: If we look at how the atav functions after it's implanted, you can see an example of a segment of the atav that was used to treat an injured femoral artery after a blast injury.

429
01:22:02.940 --> 01:22:09.860
Laura Niklason: The images in the middle and on the right-hand side show show cellular repopulation of the atav after implantation.

430
01:22:10.100 --> 01:22:22.579
Laura Niklason: as you can see at 9 months after implantation, the

atav is filled with red colored cells, which are vascular, smooth muscle cells which migrated in from the patient, turning the atav into a living artery.

431
01:22:22.710 --> 01:22:30.580
Laura Niklason: In addition, there are cells on the lumen of the vessel on the inner surface called endothelial cells, which help with blood compatibility.

432
01:22:30.700 --> 01:22:31.720
Laura Niklason: Next slide

433
01:22:34.730 --> 01:22:54.940
Laura Niklason: the pivotal phase, 3. Trial phase, 2, 3. Trial in civilians that we submitted in support of the Ntep application was a single arm trial that involved patients who were enrolled from ages 18 to 85. These were patients who suffered acute, vascular trauma and who had no vein available.

434
01:22:55.320 --> 01:23:05.530
Laura Niklason: The the endpoints were patency, limb, salvage, and infection, and also patient survival at 30 days, although we follow patients for out to 3 years

435
01:23:05.960 --> 01:23:06.950
Laura Niklason: next slide.

436
01:23:09.540 --> 01:23:28.619
Laura Niklason: In support of this application we've also submitted a real world observational study, which we did as a humanitarian effort in Ukraine to treat wartime injuries. This was a study that's still ongoing began in in 2022 in collaboration with the Ukrainian Government, and also the FDA

437
01:23:28.970 --> 01:23:53.420
Laura Niklason: Humacyte shipped vessels to 5 frontline hospitals in Ukraine to treat wartime injuries, and 19 patients were treated over a 1-year period. Of these we were able to gather retrospective data. On 16 of these patients who had injuries to the arteries of the extremities. The outcomes in this trial were the same as in the civilian trial

438

01:23:54.020 --> 01:23:55.010
Laura Niklason: next slide.

439
01:23:57.330 --> 01:24:20.499
Laura Niklason: So if we look at the trial outcomes for both the civilian and the military real world experience, our comparator. Here is the published literature in similar patients who also did not have vein, and who were treated with synthetic grafts. This comparator Benchmark was drawn from a systematic literature review over the last 20 years.

440
01:24:20.520 --> 01:24:36.090
Laura Niklason: and what you can see what's clear is that patients treated with atav did much better than similar patients treated with synthetic grafts. Specifically, the amputation rate was 4 and a half percent, whereas the synthetic graft amputation rate was over 24%.

441
01:24:36.150 --> 01:24:39.680
Laura Niklason: The conduit infection rate was very low, less than 1%.

442
01:24:39.870 --> 01:24:45.190
Laura Niklason: And the secondary patency was 91% as compared to 79%.

443
01:24:45.190 --> 01:24:47.070
Catherine Bernstein: You have 3 min remaining.

444
01:24:47.070 --> 01:24:49.589
Laura Niklason: For synthetic graphs next slide.

445
01:24:52.180 --> 01:25:13.529
Laura Niklason: So we believe that the atav really represents a substantial clinical improvement and is a new treatment option, because autologous vein. Grafts are not available in all patients, particularly in the Medicare population, where veins may have been previously harvested, or may be diseased or due to concomitant injuries. The veins are simply not available

446
01:25:14.370 --> 01:25:15.460
Laura Niklason: next slide

447
01:25:17.370 --> 01:25:33.589

Laura Niklason: in terms of clinical outcomes from the data that I've just showed you in patients who don't have vein who would have gotten a synthetic graft. The atav outcomes are actually substantially better for infection for limb salvage and also for conduit patency.

448
01:25:33.990 --> 01:25:44.819
Laura Niklason: Interestingly, as I mentioned earlier. The Atav is available off the shelf, and does not require the time to harvest vein that the gold standard autologous vein treatment does.

449
01:25:44.850 --> 01:26:11.390
Laura Niklason: In fact, if we compare the outcomes of Atev patients to similar propensity, matched patients who are civilians who received autologous vein, and this is from the Prove it registry, which is a large Us. Trauma registry. What we see is that outcomes with atav in the black column here are actually similar to outcomes that might have been seen with autologous vein, which again is the gold standard, but which was not available in the patients treated in our trial

450
01:26:12.880 --> 01:26:13.860
Laura Niklason: next slide.

451
01:26:15.750 --> 01:26:28.389
Laura Niklason: So in summary, the Atav is a 1st of its kind, and bioengineered and implantable blood vessel. It's available off the shelf. It's available to surgeons within minutes, and we don't have to injure the patient in order to procure the conduit.

452
01:26:28.830 --> 01:26:38.610
Laura Niklason: What our clinical studies have shown is that, compared to historical comparators with synthetic grafts, we outperform in terms of patency, infection, and limb salvage.

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01:26:38.910 --> 01:26:47.129
Laura Niklason: So we believe the Atev is a fundamentally new treatment option that's never been studied in this space before, and provides significant clinical improvements.

454
01:26:47.130 --> 01:26:48.289
Catherine Bernstein: 1 min remaining.

455
01:26:48.290 --> 01:26:56.350

Laura Niklason: With respect to synthetic grafts, and also is more rapidly available than autologous vein next slide.

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01:26:58.900 --> 01:27:01.729
Laura Niklason: And these are our references, and I'm done. Thank you very much.

457
01:27:04.720 --> 01:27:07.050
Drew Kasper: Thank you very much for your presentation.

458
01:27:08.270 --> 01:27:14.620
Drew Kasper: and with that we'll now move on to questions from the public. Do we have any questions from the public.

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01:27:17.290 --> 01:27:19.870
Drew Kasper: I don't have any new questions in the Q. And a.

460
01:27:20.750 --> 01:27:23.760
Drew Kasper: And let's see, here we have a hand up from

461
01:27:25.460 --> 01:27:26.884
Drew Kasper: See? I'll go ahead, and

462
01:27:28.880 --> 01:27:31.069
Drew Kasper: I'm gonna ask you to unmute

463
01:27:34.070 --> 01:27:35.560
Drew Kasper: Martin.

464
01:27:36.110 --> 01:27:37.400
Drew Kasper: Oh, there we go.

465
01:27:38.110 --> 01:27:40.919
Martin Shkreli: I had a question about the status of the FDA

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01:27:41.569 --> 01:27:45.760
Martin Shkreli: the FDA review of the application to the bla application.

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01:27:46.760 --> 01:27:55.740
Laura Niklason: Yes, the the bla remains under review, as we've stated in our quarterly earnings, calls, and other and other public announcements.

468
01:28:00.970 --> 01:28:01.420
Martin Shkreli: Thank you.

469
01:28:04.020 --> 01:28:14.139
Drew Kasper: Looks like. We have a question also in the Q. And a. What is the long term patency of the v. 0 0 5. Study alone.

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01:28:17.173 --> 01:28:23.699
Drew Kasper: I can't answer that question right off the top of my head. I don't have the Km. Curves in front of me.

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01:28:23.770 --> 01:28:52.950
Laura Niklason: Although I can say that what we observed in both the Vo. 5 and the Ukrainian study is that the secondary patency really levels off, and we after about 6 or 9 months, and we've had no further losses of patency following patients out to 3 years. So the patency of there are some early patency losses which are often due to concomitant injuries, but in the long term the atav is very durable in terms of patency.

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01:28:59.410 --> 01:29:03.080
Drew Kasper: Okay, any other questions from the public.

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01:29:04.100 --> 01:29:07.079
Drew Kasper: We have no new questions in the new tech mailbox.

474
01:29:09.090 --> 01:29:11.450
Drew Kasper: no new questions in the Q. And a.

475
01:29:12.440 --> 01:29:30.890
Drew Kasper: And there are no hands raised from attendees. So with that, if the public still has questions, feel free to raise a hand or enter it into the Q. And A. But we'll now move on to questions from Cms. Cms. Feel free to unmute and ask your questions.

476

01:29:33.760 --> 01:29:38.549
Perry Alexion: This is Perry Alexian, one of the medical officers. Thank you for your presentation. Ms. Nicholson.

477
01:29:38.720 --> 01:29:54.609
Perry Alexion: Can you further explain the meta-analysis that was used to determine the benchmarks for synthetic graphs. Specifically, the selection of the 309 patients used for comparison purposes.

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01:29:55.840 --> 01:30:20.849
Laura Niklason: Yes, thank you for that question. So this meta-analysis, the structure of this analysis was agreed to with the FDA prospectively, actually, early in 2023, but essentially the criteria for the analysis were publications between 2,002 and 2,000 and early 2023. These were publications. All of these were retrospective because there are no prospective

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01:30:21.590 --> 01:30:33.629
Laura Niklason: clinical trials in vascular trauma that have been done. Period. So all of these were retrospective studies. The requirements were that the number of patients had to be at least 5.

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01:30:33.630 --> 01:30:57.100
Laura Niklason: The quality of the papers had to be high quality by the Murad scoring, so they had to have a score of at least 4, which indicated a very low propensity for bias in the publication. This included both military and civilian injuries. It included extremity injuries and patients who were suffering non iatrogenic trauma.

481
01:30:57.170 --> 01:31:22.110
Laura Niklason: So those were at a high level. Those were the criteria. We screened more than 10,000 total papers in the world's literature, and we boiled that down to, I think, 13 total papers that were used in the meta-analysis. Actually, the meta-analysis itself is under review right now. It's out for publication, and we'll be happy to submit that publication once it comes out.

482
01:31:23.180 --> 01:31:33.629
Perry Alexion: Any accounting for improvements that may have occurred in perioperative care. Medical therapies over the last 25 years, when looking at cases that may have been done in the early 2 thousands.

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01:31:34.540 --> 01:32:00.679

Laura Niklason: So one of the sad facts of traumatic arterial repair is that very little improvement has been done in open surgical repair. There has been an advent of minimally invasive repairs that are typically used for smaller and more discrete injuries. But for patients who require open repair. The amount of true innovation over the last couple decades has been minimal.

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01:32:00.700 --> 01:32:08.790
Laura Niklason: And and I would I would say that what really supports that is that prior to this literature review that we did in 2023.

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01:32:08.930 --> 01:32:20.519
Laura Niklason: In order to understand our outcomes. We had done an earlier literature review a couple years before, and at that time we had looked at papers from 1970 through 9 through 2020,

486
01:32:20.720 --> 01:32:35.740
Laura Niklason: and the outcomes in terms of patency and limb salvage were identical over 50 years, and then over the last 20 years. So truly, I would say that in terms of open surgical repair and traumatic injury there's been little or no innovation in decades.

487
01:32:38.470 --> 01:32:58.019
Perry Alexion: Can you clarify again the intended use of atav with respect to a substitute for the synthetic grafts? Is it for all synthetic grafts? Or for when the circumstances are such that synthetic grafts may not be optimal from a perhaps contaminated wound, standpoint.

488
01:32:59.480 --> 01:33:19.429
Laura Niklason: So it's more likely the latter. If you look at the published literature on the risk of infection for traumatic injuries, obviously penetrating wounds, which are all essentially microbially contaminated, are all sort of defined as high risk.

489
01:33:19.430 --> 01:33:29.790
Laura Niklason: however, even crush injuries which have a lot of devitalized tissue are also seen as being at high risk of infection, even though they're not initially contaminated.

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01:33:29.790 --> 01:33:57.139
Laura Niklason: So if you look at the treatment guidelines for extremity, vascular trauma, those guidelines state that synthetic

grafts can be used if vein is not available as a backup option, but they are essentially never preferred, because they are viewed as being at high risk of infection, and if the conduit becomes infected, then that leads to sepsis and limb loss and other complications.

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01:33:57.140 --> 01:34:11.599
Laura Niklason: so certainly for for grossly contaminated wounds, I don't think any surgeon would preferentially put a synthetic graft in, and he would only do it if he thought the only other option was to cut off the leg.

492
01:34:14.100 --> 01:34:20.610
Perry Alexion: One last question in terms of a metric of patency, can you differentiate for me that the

493
01:34:21.150 --> 01:34:26.290
Perry Alexion: the appropriateness as a comparative metric between primary and secondary patency.

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01:34:27.340 --> 01:34:40.299
Laura Niklason: Yes, so primary patency is defined in the vascular surgery. Literature as a conduit that has maintained blood flow throughout the duration, and has had no interventions to maintain or restore blood flow.

495
01:34:40.680 --> 01:34:53.560
Laura Niklason: Secondary patency, on the other hand, includes a conduit that has maintained blood flow for the duration, but that those conduits may have had an intervention, or a thrombectomy, or or an angioplasty? Or what have you?

496
01:34:53.910 --> 01:35:19.969
Laura Niklason: When we talk about secondary? We measured both primary and secondary patency in our study, but for purposes of looking at the synthetic graft comparator in that surgical literature, it was really only secondary patency that was reported. And so that's why, when we're talking about head-to-head outcomes, we compared our secondary patency with Atav to the secondary patency with synthetic grafts.

497
01:35:22.000 --> 01:35:23.600
Perry Alexion: Okay, thank you. That's all I have.

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01:35:25.410 --> 01:35:31.879
Drew Kasper: And we did get a question from the public as well during this time in our QA

499
01:35:32.100 --> 01:35:39.690
Drew Kasper: question is, can you help me understand how Atef compares to Artiraft, which is FDA approved in trauma.

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01:35:41.660 --> 01:35:44.291
Laura Niklason: So. We don't have any

501
01:35:45.270 --> 01:36:13.710
Laura Niklason: good publications. The number of publications and artiraft in trauma is extremely limited, so it's difficult for me to comment. I do think that Artiraft can have a higher risk of aneurysmal failure because it is animal tissue that's glutaraldehyde fixed and so long-term patency and long-term mechanical durability are substantially lower than they are, I believe, for atav.

502
01:36:13.710 --> 01:36:34.519
Laura Niklason: you know, in the arterial circulation we have publications going out 6 years which shows no aneurysm and no mechanical degeneration whatsoever. And that's just not true with xenografts all xenografts, whether they're pig derived or cow derived, and they're glutaraldehyde fixed they all have some important rate of mechanical degeneration and aneurysm.

503
01:36:39.830 --> 01:36:43.780
Drew Kasper: Thanks. We'll skip back to Cms. For additional questions.

504
01:36:45.670 --> 01:36:55.620
Adina Hersko: Hi, just to follow up on Dr. Luxian's question. Earlier you had mentioned that primary patency was not assessed in previous studies for synthetic grafts.

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01:36:55.970 --> 01:37:05.809
Adina Hersko: Do you have any idea why that would be? Or are there any studies that share primary patency, and any idea how H Hf. Compares to those.

506
01:37:06.740 --> 01:37:30.120
Laura Niklason: So there was one of the high quality studies. There

was one paper that reported secondary primary patency, and I believe the primary patency reported in that one paper was 78%. If I remember correctly, as far as why primary patency is not reported. That's a little bit speculative. What I can say is that in the trauma surgical literature

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01:37:30.120 --> 01:37:41.580
Laura Niklason: the authors of these papers tend to be trauma surgeons, as opposed to vascular surgeons and trauma surgeons are more focused on the ultimate patency of the conduit.

508
01:37:41.660 --> 01:38:00.910
Laura Niklason: and less focused on whether or not an intervention had to be done, whereas the vascular surgical literature, by sort of habit they tend to report both primary and secondary patency. But my sense is that in terms of sort of the clinical relevance, trauma surgeons focus more on secondary patency.

509
01:38:02.240 --> 01:38:03.020
Adina Hersko: Thank you.

510
01:38:07.520 --> 01:38:10.929
Drew Kasper: There any other questions from Cms. Or the public?

511
01:38:14.270 --> 01:38:16.390
Drew Kasper: I have no questions in the Q. And a.

512
01:38:17.060 --> 01:38:22.139
Drew Kasper: No raised hands and no new questions in the new tech mailbox.

513
01:38:23.540 --> 01:38:27.119
Drew Kasper: Okay, well, thank you.

514
01:38:27.920 --> 01:38:36.369
Drew Kasper: We will now move on to hear from presenters for Rustigo. You may now unmute your phone and introduce yourself.

515
01:38:36.540 --> 01:38:49.729
Angela Ting: Great. Thank you for the opportunity to share information around Restigo for the ntap application. My name is Angela Ting, and

for the purpose of disclosure. I'm a full time employee of Ucb. Pharmaceutical next slide.

516
01:38:51.620 --> 01:39:06.459
Angela Ting: The purpose of this presentation is to provide information around generalized myasthenia gravis and restigo in support of ntap status. The use of restigo in any way other than specified by the product. Labeling is not recommended by Ucb. Next slide

517
01:39:08.190 --> 01:39:21.429
Angela Ting: I will be walking us through a brief overview of myasthenia gravis, or Mg. The mechanism of disease, and how restigo meets a previously unmet medical need for certain Gmg. Patients next slide.

518
01:39:23.183 --> 01:39:24.210
Angela Ting: One more

519
01:39:26.000 --> 01:39:43.219
Angela Ting: great. So I'll start with myasthenia gravis, or Mg. Is a condition where the muscle loses function and weakens in ways that potentially can be life threatening for patients. Mg. Occurs when a person's immune system mistakenly attacks the communication between the nerve and the muscle

520
01:39:43.370 --> 01:40:10.769
Angela Ting: in Mg. The body inappropriately produced certain antibody that blocks or destroyed the receptors on the muscle which prevents key messages from being delivered properly resulting in muscles not contracting this disease can affect muscles throughout the entire body, including, but not limited to, the face, muscles, throat, limb, or respiratory muscles, which can cause people to have difficulty swallowing, moving.

521
01:40:11.380 --> 01:40:28.400
Angela Ting: moving, or in severe cases breathing. The most common type of pathogenic or the bad antibody is the acetylcholine receptor antibodies. Although there is a second specific type, it's less common. It is the muscle specific kinase or the musk antibody.

522
01:40:28.570 --> 01:40:29.590
Angela Ting: Next slide

523
01:40:31.440 --> 01:40:52.399
Angela Ting: in terms of demographics for mg, about 60% of mg, patients would be medicare beneficiaries with a mean age of diagnosis around 60. And there is a disproportionate distribution of it. Typically happens younger and female and older, for males. Next slide.

524
01:40:55.680 --> 01:41:07.509
Angela Ting: Now, among the autoantibody subtype, I want to focus on musk while musk Mg. Is more rare. It is also more severe and more difficult to treat

525
01:41:07.510 --> 01:41:32.120
Angela Ting: patient with musk. Antibody has higher disease, burden, and limited treatment options. There were no FDA approved therapies for musk gmg. Prior to the approval of rustigo, standard of care. Therapies like pyridosigmine, may not be effective, and could actually lead to symptom worsening. Similarly, immunosuppressants like azathioprine or rituximab which represents the main

526
01:41:32.120 --> 01:41:42.690
Angela Ting: mainstay of treatment for these patients has not been FDA approved, and there may also have been safety concerns with long-term use of these agents

527
01:41:43.800 --> 01:41:44.880
Angela Ting: next slide.

528
01:41:46.850 --> 01:42:09.809
Angela Ting: Now I also want to highlight the race of symptom worsening that could lead to rescue therapy or hospitalization while Mg. Patients are on standard of care therapy. This shows that roughly, about 40% of patients continues to have Mg, exacerbation and may benefit from new or targeted treatment. Approach.

529
01:42:10.943 --> 01:42:13.140
Angela Ting: I'll move on to the next slide.

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01:42:15.250 --> 01:42:34.450
Angela Ting: Next I'll go over briefly, go over the mechanism of disease. So this slide in a nutshell. In patients in healthy patients, signals are transmitted between nerve and muscle leading to muscle

movement. I won't go into the details of the actual mechanism of action in the next slide.

531
01:42:35.800 --> 01:43:00.759
Angela Ting: This shows a depiction of antibody in patients with Mg. The antibodies prevent signal transmission between the nerve and muscle, and it could destroy the receptors or prevent the signal transmission, both of which can lead to weakening of muscle contraction. The musk protein helps maintain the communication point of the acetylcholine receptor between the nerve and the muscle.

532
01:43:00.760 --> 01:43:09.150
Angela Ting: and when they're attacked by the musk antibodies. There are less receptors to receive the signals which can cause muscle weakness

533
01:43:09.280 --> 01:43:15.270
Angela Ting: and then moving on to the next slide, and one more.

534
01:43:16.440 --> 01:43:39.439
Angela Ting: So I'll start a focus on restigo. It's an fcrm blocker. It's indicated for both acetylcholine receptor or musk antibody generalized myasthenia gravis. It is the only product approved for musk Antibody, Gmg. There are 3 dosing options available and is administered as a subcutaneous infusion. Once weekly for 6 weeks.

535
01:43:39.910 --> 01:43:41.060
Angela Ting: Next slide

536
01:43:42.760 --> 01:44:10.330
Angela Ting: from a moa perspective. The fcrn recycles antibodies both good and bad, so they end up staying in the system longer. Rostigos prevents the fcrn from binding to the antibodies, because the receptor is bound by the drug. The antibodies cannot recycle back into circulations, or thus are eliminated from the system in turn. The symptoms of Gmg are then reduced, and muscle can resume more normal function.

537
01:44:10.700 --> 01:44:11.860
Angela Ting: Next slide

538
01:44:14.010 --> 01:44:40.610

Angela Ting: in our pivotal phase, 3. Study demonstrating efficacy. We evaluated the changes in Mgadl or the activities of daily living. It's an FDA accepted patient, reported outcome questionnaire that measures the ability to breathe, chew, swallow, and do other daily activities. We studied both acetylcholine receptor, positive and musk positive patients.

539
01:44:40.610 --> 01:45:09.100
Angela Ting: It's important to note that in this study restigo was not compared against a treatment naive placebo group rather patients in the placebo and treatment groups were allowed to remain on their standard of care therapy, such as immunosuppressive therapy, corticosteroids or paritostigma. They were then randomized to either rustigo or placebo. So this study is looking at the benefits of restigo beyond just the standard of care therapies

540
01:45:09.490 --> 01:45:10.660
Angela Ting: next slide.

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01:45:12.530 --> 01:45:41.749
Angela Ting: Now, when we look at the results. It was both statistically significant, and it also demonstrated a clinically meaningful reduction in Mgadl. At day 43. The endpoints were achieved in both achr and musk patients. Restigo showed a 2.5 9 reduction in Mgadl on top of the standard of care therapy, demonstrating more than one or more activities of daily living improvement.

542
01:45:42.480 --> 01:45:44.160
Catherine Bernstein: You have 3 min remaining.

543
01:45:44.160 --> 01:46:09.500
Angela Ting: Okay, thank you. Now, building on the outcomes in a subgroup analysis, the musk group showed 7.3 and 4.1 improvement in the 7 and 10 milligram respectively, over the standard of care therapies that had a worsening of mgadl of 2.2 8 increase. So they actually had worsening of symptoms next slide.

544
01:46:10.800 --> 01:46:19.939
Angela Ting: and this translated to 100% responder rate in patients having over a 2 point reduction in Mgadl in the musk patients

545
01:46:20.540 --> 01:46:21.650
Angela Ting: next slide.

546
01:46:23.780 --> 01:46:47.080
Angela Ting: Now, as I mentioned earlier, restigo is a subcutaneous infusion. Once weekly for 6 weeks in patients with severe symptoms that requires hospitalization, the average length of hospital stay is roughly 2 weeks in Mg. Medicare patients. This would mean 2 doses would be administered per average inpatient stay with the treatment continuing after discharge. Next slide

547
01:46:48.990 --> 01:46:58.329
Angela Ting: in terms of safety, restigo may increase the risk of infection, safety with life attenuated vaccines are unknown, and additional safety information can be found in the Pi

548
01:46:59.230 --> 01:47:01.500
Angela Ting: last my last slide.

549
01:47:03.530 --> 01:47:28.490
Angela Ting: So, in conclusion, we believe Restigo meets the 3 criteria for ntap. This was newly approved. On June 26, th 2023. It shows substantial clinical improvement over standard of care, therapies and Gmg. And it is the only therapy approved for patients with musk positive gmg. Although not addressed in this clinical presentation, it also meets the threshold, supported by the information

550
01:47:28.490 --> 01:47:36.729
Angela Ting: submitted in the merit submission. So we request that Cms. Grants ntap status for Rustigo, and I welcome any questions at this time.

551
01:47:41.420 --> 01:47:45.190
Drew Kasper: Thank you for your presentation. Are there any questions from the public

552
01:47:45.500 --> 01:47:48.889
Drew Kasper: as a reminder? This can include other applicants as well.

553
01:47:54.680 --> 01:47:57.330
Drew Kasper: We don't have any questions in the Q. And a.

554

01:47:57.860 --> 01:48:00.389
Drew Kasper: We don't have any raised hands from attendees.

555
01:48:01.950 --> 01:48:05.359
Drew Kasper: and we don't have any new questions in the new tech mailbox.

556
01:48:05.600 --> 01:48:18.710
Drew Kasper: so we will open it up to Cms questions at this time, however, if anyone from the public has a question during this time feel free to use that Q. And a. To enter your question or raise a hand.

557
01:48:19.010 --> 01:48:22.170
Drew Kasper: and we'll now open to questions from Cms.

558
01:48:23.360 --> 01:48:25.160
Drew Kasper: Folks can go ahead and unmute.

559
01:48:34.080 --> 01:48:37.190
Beth Koller: Yes, this is Dr. Kohler.

560
01:48:38.530 --> 01:48:39.759
Beth Koller: Can you hear me?

561
01:48:39.760 --> 01:48:40.440
Angela Ting: Yes.

562
01:48:41.720 --> 01:48:45.959
Beth Koller: Okay. So I have a 3 particular points.

563
01:48:46.660 --> 01:48:51.560
Beth Koller: I have 3 particular points that I'd like to make, and I'll list them all at once.

564
01:48:52.070 --> 01:48:59.629
Beth Koller: I'm hoping that you can comment on the discordance of the patient numbers in the Brill 2023 paper.

565

01:48:59.780 --> 01:49:12.369
Beth Koller: and in the FDA Review. This regards the musk patients, the seronegative patients, and the total patient numbers which were less than the stated 200.

566
01:49:13.440 --> 01:49:17.629
Beth Koller: The second comment is, I'm hoping that you can

567
01:49:17.830 --> 01:49:20.620
Beth Koller: comment on the use of a post hoc.

568
01:49:20.770 --> 01:49:24.649
Beth Koller: 97.5% confidence interval

569
01:49:25.080 --> 01:49:30.740
Beth Koller: versus the usual 95% confidence interval for statistical significance.

570
01:49:30.890 --> 01:49:43.890
Beth Koller: And how such statistical significance was found in musk, positive patients, of which there were total of only 16,

571
01:49:44.530 --> 01:49:47.979
Beth Koller: and how the statistical significance

572
01:49:48.710 --> 01:49:56.479
Beth Koller: was found only in those treated with the 7 milligram dose, but not the 10 milligram dose

573
01:49:56.610 --> 01:50:01.180
Beth Koller: for the patient reported Mg. Adl.

574
01:50:01.290 --> 01:50:07.450
Beth Koller: Activities of daily living tool, but not for either dose for the objective.

575
01:50:07.710 --> 01:50:11.910
Beth Koller: Qmg. Assessment and number 3.

576

01:50:12.010 --> 01:50:15.100
Beth Koller: Please comment on validity issues.

577
01:50:15.280 --> 01:50:27.570
Beth Koller: With these endpoints neither the Qmg. Nor the Mgadl were based on clinically meaningful differences established a priori.

578
01:50:27.980 --> 01:50:30.319
Beth Koller: The objective Qmg.

579
01:50:30.440 --> 01:50:36.170
Beth Koller: Was assessed around 1987, using 20 patients.

580
01:50:36.770 --> 01:50:57.030
Beth Koller: The patient reported outcome survey. The Mgadl was assessed in 1999, along with the Qmg. Looking at Concordance. They did this at a single clinic, and there were 156 patients, but some of these patients were assessed more than one time.

581
01:50:57.440 --> 01:51:05.460
Beth Koller: and the reported correlation coalition was very modest at 0 point 5 8, and these are my comments.

582
01:51:07.130 --> 01:51:31.339
Angela Ting: Great. Thank you for those comments. Those are great questions. So I'll start with the 3rd 1 1st around the validity issue of Qmg. Or Mgadl. Recognizing that these were originally developed back in 1987 small patient population. There has been several, I guess, studies out there more recently. There's

583
01:51:31.340 --> 01:51:55.549
Angela Ting: there's 1 that's looking at the correlation of Mgadl to healthcare utilization. And that's a manuscript in progress. But the poster has been presented at either Aanem or one of the Neurology Conference, but it does show that there is a correlation between a reduction in Mgadl as well as to the rates of Mg. Exacerbation.

584
01:51:55.550 --> 01:52:20.410
Angela Ting: So there is a correlation to healthcare outcome when it comes to using these measures. In addition, we also had. So Mgadl was our primary endpoint. Qmg. Was our secondary endpoint. We also looked at Mgpro and also several other skills that did show statistical

significance. And there has been data

585
01:52:20.410 --> 01:52:28.919
Angela Ting: out there that shows there is a high correlation of improvement in those scales to the Qmg. As well as Mgadl.

586
01:52:29.657 --> 01:52:36.600
Angela Ting: I'm not sure if that addresses your questions around the validity, or if having to follow up with additional

587
01:52:40.400 --> 01:52:41.539
Angela Ting: sorry. Hello!

588
01:52:44.530 --> 01:52:45.400
Angela Ting: Hello!

589
01:52:51.890 --> 01:52:57.689
Drew Kasper: Looks like Dr. Kohler may be experiencing some issues with microphone there.

590
01:53:03.920 --> 01:53:07.999
Drew Kasper: We'll give it a little bit here.

591
01:53:10.960 --> 01:53:17.449
Drew Kasper: Okay, Dr. Kohler, I see now you're muted in zoom. So if the mic is working, it might just be a zoom mute. Now.

592
01:53:18.390 --> 01:53:19.899
Drew Kasper: there we go. You're unmuted.

593
01:53:29.819 --> 01:53:34.310
Drew Kasper: Yeah, we don't have audio from you Dr. Kohler.

594
01:53:35.790 --> 01:53:37.259
Drew Kasper: Not sure what happened there.

595
01:53:42.420 --> 01:53:49.540
Drew Kasper: Perhaps you. You could chime in to test now and then, Dr. Kohler, and in the meantime

596
01:53:51.210 --> 01:53:57.829
Drew Kasper: Did you want to perhaps address Dr. Ting some of the other issues or questions? There.

597
01:53:57.830 --> 01:54:15.860
Angela Ting: Yeah, for the other 2. Would it be possible for me to follow up with Dr. Kohler? I'd like to have input from our biostats team who conducted the the statistical analysis and and get a response back to Dr. Kohler.

598
01:54:16.920 --> 01:54:25.520
Drew Kasper: Oh, sure, yeah, and we have. You know the ability to submit written comments post town hall up until Monday at 5.

599
01:54:26.270 --> 01:54:27.375
Drew Kasper: So

600
01:54:29.370 --> 01:54:36.799
Drew Kasper: The instructions for that are pretty simple. It's just submitting to the ntep mailbox, but you'll see that at the tail end of the agenda.

601
01:54:36.800 --> 01:54:37.530
Angela Ting: Okay.

602
01:54:44.170 --> 01:54:46.869
Drew Kasper: Are there other questions from Cms.

603
01:54:48.130 --> 01:55:02.989
Adina Hersko: Hi, this is Adina Hersko with Cms. I have a couple questions as well. Can you explain? I don't know if you have any any idea about this. But how is the mgadl selected as the primary endpoint? Does a patient reported outcome

604
01:55:03.100 --> 01:55:06.219
Adina Hersko: versus the others that are that are more objective.

605
01:55:06.770 --> 01:55:33.729
Angela Ting: Yeah, I think historically, I guess so. A couple of the

last large randomized Mg, studies have used Mgadl as the primary outcome, and in our discussion with, I think, the FDA. We felt that that was more of an appropriate endpoint, and having Qmg. As a secondary endpoint. But both measures have really strong correlation to each other. So

606
01:55:34.000 --> 01:55:43.869
Angela Ting: in our phase, 2 studies we had used Qmg as the primary endpoint. But for our phase 3 you know. After discussion we just selected the Mgado.

607
01:55:45.070 --> 01:56:06.189
Adina Hersko: Thank you. I also noticed in this presentation you focused on the my Karen G study, which is compared to placebo. But, as I'm sure, you know there are many treatments approved for myasthenia gravis. Do you have any comparative outcomes to those to demonstrate that restigo is a substantial clinical improvement over those.

608
01:56:06.190 --> 01:56:23.859
Angela Ting: Yeah. So I think one of the key points with mycareng is that in order for patients to be enrolled in the study, they were required to be on stable doses of standard of care, mg. Treatment, so that includes steroids, immunosuppressive therapies as well as paritostigmine. So patients were not

609
01:56:23.920 --> 01:56:38.310
Angela Ting: purely on placebo, and not treated with anything. So in comparison to the standard of care therapy, we do see a clinically, a statistical difference in terms of the Adl. Improvement on top of the standard of care.

610
01:56:38.670 --> 01:56:47.919
Adina Hersko: So there! There were a bunch of treatments that were excluded, of course, from this trial. The more recent therapies, I mean there. There are quite a few, so.

611
01:56:47.920 --> 01:57:12.019
Angela Ting: Yeah. So the more recent therapies. One, if we're if we're talking about the complement inhibitor this, this would be because the complement. Inhibitors are macrocyclic monoclonal antibodies. So there there would potentially be a drug interaction, and they would be washed out with with concurrent use. So they wouldn't be able to be included

612
01:57:12.020 --> 01:57:32.509
Angela Ting: in the study. But then Rituximab is typically used as last line. So those are also ones that we didn't include in the study. But yes, there's no head-to-head against the other fcrns or complement inhibitor. But those products are not approved for musk. Positive. Mg.

613
01:57:33.910 --> 01:57:40.170
Adina Hersko: Okay, so is, is the ntap application focused on on the musk patients? Or is it just in general for.

614
01:57:40.390 --> 01:57:41.120
Angela Ting: Yeah.

615
01:57:41.120 --> 01:58:08.280
Angela Ting: So I think we submitted both. One is that there is clinical improvement over standard of care which includes the therapies that I listed earlier, but specifically for musk. It's in a population where there isn't an FDA approved therapy. And and those patients also the way our study was designed. It's the same population that's being studied. So it's both the Achr and musk patient.

616
01:58:10.180 --> 01:58:10.980
Adina Hersko: Thank you.

617
01:58:17.650 --> 01:58:20.539
Drew Kasper: Are there any other questions from Cms or the public.

618
01:58:22.730 --> 01:58:28.459
Adina Hersko: True. I don't know if Dr. Kohler could maybe disconnect her headset and just talk over the computer. Maybe that would help.

619
01:58:34.330 --> 01:58:40.950
Drew Kasper: See her kinda leaning into the computer, but we still can't hear.

620
01:58:40.950 --> 01:58:42.869
Adina Hersko: You can just unmute Dr. Kohler.

621
01:58:59.380 --> 01:59:01.300
Adina Hersko: No, it's look in here.

622
01:59:04.460 --> 01:59:10.730
Drew Kasper: Yeah, it's looking like she's got an ongoing tech issue. And something happened there.

623
01:59:17.590 --> 01:59:23.790
Drew Kasper: okay, yeah, I think we'll just have to rely on

624
01:59:25.320 --> 01:59:27.520
Drew Kasper: written commentary to follow up,

625
01:59:32.200 --> 01:59:38.179
Drew Kasper: And if there are questions that would help with the

626
01:59:39.060 --> 01:59:44.417
Drew Kasper: commentary and follow up you could reach out to us as well.

627
01:59:45.600 --> 01:59:52.050
Drew Kasper: If there are things that you would like to clarify regarding Dr. Fuller's inquiries.

628
01:59:52.870 --> 01:59:54.140
Angela Ting: Will do. Thank you.

629
01:59:55.810 --> 02:00:01.789
Drew Kasper: Thanks any other last questions.

630
02:00:02.730 --> 02:00:06.599
Drew Kasper: There are no questions in the Q. And a. And no raised hands.

631
02:00:08.450 --> 02:00:14.740
Drew Kasper: and no new questions in the new tick mailbox. So with that

632
02:00:15.000 --> 02:00:24.080
Drew Kasper: we will now hear from presenters for graphipacs formerly known as Triosulphan. You may now unmute your phone and introduce

yourself.

633
02:00:31.370 --> 02:00:36.270
Mark Fosdal: I'm pushing my! Do you need to allow me to turn my video on.

634
02:00:37.736 --> 02:00:43.119
Drew Kasper: You're welcome to turn your video on camera is optional. But we do hear you mark.

635
02:00:43.120 --> 02:00:48.160
Mark Fosdal: I'm not. I'm unable to turn my video on is what I'm trying to send. I'm pushing the video.

636
02:00:50.510 --> 02:00:53.460
Drew Kasper: Okay, there we go. Oh, there you are! Alright!

637
02:00:53.460 --> 02:00:54.480
Mark Fosdal: Thank you for that.

638
02:00:55.360 --> 02:01:18.899
Mark Fosdal: Okay, well, thank you for inviting me. My name is Mark Foster. I'm the clinical director at Pedexus prior to my time in industry. I was working at the Fred Hutch Cancer Research Center here in Seattle, where I have experience with triosulphan in the clinical trials, and I thank you for this opportunity today to talk to you about Triosulf. And as a conditioning agent prior to an allogenetic transplant for hematological malignancies. Next slide, please.

639
02:01:20.230 --> 02:01:41.260
Mark Fosdal: Today I'm going to talk to you about the Triosulphan as this novel transformative agent. And I'm going to mention that triosulphan has addressed an unmet need by minimizing the toxicity while maximizing the efficacy. This comes from multiple peer reviewed published papers describing triosulphan based conditioning as this reduced toxicity conditioning regimen.

640
02:01:41.460 --> 02:02:02.249
Mark Fosdal: And it's reflected, a paradigm shift we're seeing in allogeneic transplant conditioning options. I'm also going to talk to you about yourself and how it meets the ntap substantial clinical improvement criterion, and I'll focus on the Medicare population and

those with comorbidities that increase the higher risk of non-glast mortality.

641
02:02:02.370 --> 02:02:10.129
Mark Fosdal: I will use clinically significant endpoints to describe and compare Triosol, and to a variety of condition regimens as well.

642
02:02:10.480 --> 02:02:11.660
Mark Fosdal: Next slide, please.

643
02:02:13.570 --> 02:02:33.480
Mark Fosdal: Briefly, Triosulphone's regulatory status is that it was 1st granted orphan drug designation by the FDA in 2015, and if approved, triosulphone will be the 1st and only FDA approved allogenetic stem cell transplant conditioning agent for both Aml. And Mds. With adults and pediatric patients over the age of one.

644
02:02:33.810 --> 02:02:40.020
Mark Fosdal: Currently, the FDA has our Pdufa date at January 30th of 2025 next slide.

645
02:02:41.760 --> 02:02:56.200
Mark Fosdal: First, st I want to talk about the importance of an allogenetic transplant and conditioning regimen when it comes to Aml. And Mds. As you may recall, Aml. And Mds. Are usually diagnosed in their sixties and seventies, which is certainly within the Medicare population.

646
02:02:56.590 --> 02:03:10.389
Mark Fosdal: Allogeneic transplant is the sole curative option for most of these patients with Aml. Mds. That need an allogeneic transplant, and it has shown superior overall survival than with just chemotherapy alone.

647
02:03:10.840 --> 02:03:37.279
Mark Fosdal: Conditioning regimens prior to an allo transplant are important for several different reasons. One. It ablates the bone marrow and makes room for a new graft to come in 2. It eradicates residual disease, and 3. It blunts the patient's immune system to prevent this graft failure of. When a new graft comes in from an Hla donor that causes this graft versus leukemia effect. And that's what makes it unique from standard chemotherapy.

648
02:03:37.520 --> 02:04:02.939
Mark Fosdal: So previously available agents and regimens for L transplant conditionings has created an unmet need for conditioning treatment that minimizes the toxicity while maximizing the efficacy. And this is especially true for the medicare population. So because triosulphan is uniquely as it uniquely bypasses the liver metabolism. It does reduce this type of treatment related toxicity. Next slide.

649
02:04:05.830 --> 02:04:23.139
Mark Fosdal: So triosulphan again addresses this unmet need in allogenetic conditioning regimens, and I 1st want to talk to you about the 2 general types of conditioning regimens that's been around for decades. There's the myeloablative conditioning, also called a Mac, and a reduced intensity conditioning also called a Ric.

650
02:04:23.270 --> 02:04:53.089
Mark Fosdal: A Mac based regimen is exactly what it sounds. It's myeloblative, and it eradicates the disease, and it's usually meant for younger fit patients. The good news about a Mac is, it has a lower rate of relapse. The not so good news is, it has a higher rate of non-relapse mortality. For that reason Medicare patients tend to lean towards and get the reduced intensity conditioning regimen where the non-relapsed mortality is minimized, but the rate of relapse goes up and their overall survival does go down.

651
02:04:53.260 --> 02:05:18.610
Mark Fosdal: Triosulphan was developed to address the significant and growing need for conditioning regimens that minimize the toxicity while maximizing the efficacy. Now, what I mean by that is that triosulphan lowers the non-relapse mortality like a ric, but it does not increase the risk of relapse, and this, again, is defined by this reduced toxicity, conditioning regimen from a 2020 paper that we submitted with our application next slide.

652
02:05:20.500 --> 02:05:33.680
Mark Fosdal: It has received widespread recognition that true self and addresses this unmet need. And there's a sampling of quotes that you can read at another time. I don't have the time to go into these now, but this has been embraced by a wide variety of authors. Next slide

653
02:05:35.580 --> 02:05:41.330
Mark Fosdal: so Triosulphan meets the ntap. Substantial clinical improvement criterion with 2 claims.

654
02:05:41.650 --> 02:06:07.520
Mark Fosdal: claim. One triosulphan offers a treatment option for allogenetic transplant conditioning for older, or those with comorbid illnesses who are ineligible for other currently available conditioning regimens like the Mac related regimens that we talked about. There have been multiple published peer review studies that demonstrate that triosulphan addresses the widely recognized need for the improved allotransplant conditioning for this Medicare population

655
02:06:08.800 --> 02:06:09.730
Mark Fosdal: next slide.

656
02:06:12.190 --> 02:06:22.330
Mark Fosdal: Now these are again, are some quotes from a wide variety of authors, and once again, one of the quotes is that true self and treatment is a promising strategy for stem cell transplantation in patients

657
02:06:22.430 --> 02:06:27.240
Mark Fosdal: with Aml and Mds. Who are ineligible for Mac based regimen.

658
02:06:27.730 --> 02:06:32.280
Mark Fosdal: Next slide claim. 2

659
02:06:32.650 --> 02:06:56.830
Mark Fosdal: triosulphan-based conditioning has shown superior outcomes in event-free survival overall survival, non-relapsed mentality and significant reduction in several adverse events. And I'll go on to talk to you about clinically meaningful endpoints, comparing triosulphan to other conditioning regimens. And I'll also emphasize some of those studies. Talk about shorter hospitalizations or readmissions.

660
02:06:57.010 --> 02:06:57.990
Mark Fosdal: next slide.

661
02:07:00.110 --> 02:07:30.039
Mark Fosdal: The 1st study I'd like to talk about demonstrates that true Sulfan was superior in event-free survival, overall, survival and non-relapse mortality. In one of the larger peer reviewed phase 3 multicenter studies in Europe in a randomized, controlled trial. Now,

once again, this patient population could not get a myeloblative conditioning regimen. The Median age was 60, and what's called the Comorbidity index was 3 or higher. And that basically means that they have comorbidity issues that put them at risk for a higher non-relapse mortality.

662
02:07:30.250 --> 02:07:45.750
Mark Fosdal: and what they did here was that they used triosulphan 10 grams per meter, squared daily for 3 days with Fludarabine, and it randomized patients to receive the standard care at the time of Fludarabine, with 2 days of busolphan otherwise known as Flubu. 2.

663
02:07:46.000 --> 02:08:05.009
Mark Fosdal: What's interesting about this study of 570 patients is that 27% of the patients were between the ages of 65, and 74. Now, typically, this is the group of people that are excluded from such trials because of their higher rate of non-relapsed mortality that skews the data. Thank you.

664
02:08:05.150 --> 02:08:06.109
Mark Fosdal: Next slide.

665
02:08:07.430 --> 02:08:11.060
Mark Fosdal: The primary endpoint of this event-free survival at 3 years

666
02:08:11.170 --> 02:08:19.819
Mark Fosdal: showed superiority with triosulphan at 59.9% or 59.5% compared to Busolphan at 49.7%

667
02:08:20.590 --> 02:08:21.549
Mark Fosdal: next slide.

668
02:08:22.540 --> 02:08:51.649
Mark Fosdal: Some of the relevant secondary endpoints that I wanted to point out was clinically significant. Graft versus host disease and known complication. Post-transplant was higher in Busolphan, which requires more immunosuppression and led to a statistically higher death rate due to infections. Now that impacted the 9 11 mortality in the lower over survival and the lower event-free survival compared to triosulphan. So in those areas Triosulphan showed superiority with less incidence of Gphd. In this study.

669
02:08:51.660 --> 02:08:58.549
Mark Fosdal: Now there is no difference in relapse in this study, and there is no difference here again, with serious adverse events that were not that life threatening

670
02:08:58.570 --> 02:08:59.830
Mark Fosdal: next next slide.

671
02:09:01.260 --> 02:09:19.170
Mark Fosdal: I wanted to end talking about some international studies and some in Canada that looks at Aml. Mds patients in the older patient population and looks at Fludarabine and compared to a wide variety of conditioning regimens that are used. Melphin based regimens

672
02:09:19.270 --> 02:09:40.199
Mark Fosdal: incorporating Cytoxin, incorporating Tbi or total body irradiation, a wide variety of Rick and Mac based regimens compared to trio flu, had a consistent theme of where flu trio performed better with a lower relapsed mortality that translated into a higher overall survival

673
02:09:40.570 --> 02:09:41.470
Mark Fosdal: next slide.

674
02:09:43.200 --> 02:10:02.730
Mark Fosdal: and Dr. Shinomi, this top paper quoted was quoted to saying, flu trio is associated with a similar low relapse rate as a Mac and a similar low non-relapse mortality as a Ric resulting in an improved overall survival. And that is again, by definition, the reduced toxicity conditioning where you're getting the best of both.

675
02:10:03.970 --> 02:10:05.120
Mark Fosdal: Next slide, please.

676
02:10:05.900 --> 02:10:31.669
Mark Fosdal: My last slide. I wanted to again point out that these 2 studies showed superiority in event-free survival, but they also mentioned that the percent of patients requiring at least one hospital readmission was significantly lower with the Triosulphan and the European study in this bottom showed that with severe mucositis and vod that made an impact in the duration of hospitalization, also favoring triosulphan

677
02:10:32.110 --> 02:10:33.050
Mark Fosdal: next slide.

678
02:10:34.260 --> 02:11:03.970
Mark Fosdal: So today I was able to talk to you about triosulphan as a novel, transformative conditioning agent used for Lgena transplant with hematological malignancies. I mentioned that triosulphan addressed an unmet need by minimizing the toxicity, while maximizing the efficacy also known as reduced toxicity conditioning. I've discussed significant primary endpoints that are used quite often in the Medicare population, and how triosulphan has shown superiority in this patient population in a wide variety of regimens.

679
02:11:04.100 --> 02:11:06.610
Mark Fosdal: Thank you very much, and I'll take your questions.

680
02:11:08.850 --> 02:11:11.339
Drew Kasper: And thank you very much for your presentation.

681
02:11:11.900 --> 02:11:16.329
Drew Kasper: We'll now open it up to questions from the public.

682
02:11:21.600 --> 02:11:27.860
Drew Kasper: Don't see any questions in the QA. Yeah. And attendees do not have any raised hands.

683
02:11:30.020 --> 02:11:33.695
Drew Kasper: We don't have any new questions in the new tech mailbox.

684
02:11:34.200 --> 02:11:39.809
Drew Kasper: So with that, then we'll move on to opening up to Cms questions

685
02:11:40.230 --> 02:11:48.770
Drew Kasper: with the caveat that any public questions can still come in through the Q. And a. Or through a raised hand for attendees.

686
02:11:50.170 --> 02:11:55.680
Drew Kasper: and with that Cms can go ahead and unmute and ask your

questions.

687
02:11:57.230 --> 02:12:22.319
Adina Hersko: Thank you for your presentation. This is Adina. From Cms. I had a question. You had a couple of studies there, a bunch of different studies comparing to different regimens. But were any of those comparing to other reduced toxicity regimens? It's my understanding that you know, there's not just triosulphan that's considered reduced toxicity. But there's others as well. Intermediate doses of tbi, higher doses of the sulfon, etc.

688
02:12:22.580 --> 02:12:38.460
Mark Fosdal: Yes, again, the concept of reduced intensity and myeloblative regimens is defined back in 2,009, the 2020 paper that creates a new score that the condition, the Tci transplant conditioning intensity

689
02:12:38.590 --> 02:13:06.470
Mark Fosdal: identifies some types of Rtc types of regimens beyond just triosulphan. So yes, some of those studies were used and compared to triosulphan and with Medicare population, for example, with malphalan, Malphan tends to have more gut toxicity, for example. And so yes, in those studies at least the one that I'm thinking of that we've submitted. Triosulphan was shown to be more effective in less toxicity in the Medicare population or those older patients as well.

690
02:13:06.670 --> 02:13:10.179
Mark Fosdal: but that had been submitted with our with our application.

691
02:13:10.500 --> 02:13:15.709
Adina Hersko: Can you just clarify which one specifically was one of these reduced toxicity regimens.

692
02:13:16.320 --> 02:13:21.340
Mark Fosdal: I will have to, I think. You can go back a couple of slides. I could point to them

693
02:13:23.322 --> 02:13:25.730
Mark Fosdal: the 1st one more.

694
02:13:26.140 --> 02:13:28.073

Mark Fosdal: One more. There we go,

695
02:13:28.740 --> 02:13:34.669
Mark Fosdal: And once one other slide here. If you go back to I'm sorry. Go forward a couple of slides, please.

696
02:13:36.430 --> 02:14:00.460
Mark Fosdal: One more. So here you have the Shimoni paper, the top one where it's trio flu compared to a wide variety of ric and a wide variety of Mac regimens. There was too many to look at. This, I believe, was a retrospective study looking at commonly used Ric and Mac based regimens as it was compared to a flu day or triosulphan. Is that the kind of example you'd like.

697
02:14:00.900 --> 02:14:11.290
Adina Hersko: So. No, I was. I was looking more, for you know, besides, for the Rick and the Mac there's also those other ones that are considered like true itself, and, like you, were describing, to be reduced toxicity, so kind of like in between.

698
02:14:11.290 --> 02:14:32.239
Mark Fosdal: I'd have to look at the 2020 paper and see which ones the Tci scoring, as you may recall, is one through 6. Anything between the score of 2 and 4 were considered intermediate, and I do not have that list in front of me. I can get back to you through our letter to let you know which ones were in that Tci score over the intermediate phase. If that would be helpful.

699
02:14:32.620 --> 02:14:33.790
Adina Hersko: Thank you. Perfect.

700
02:14:40.570 --> 02:14:42.420
Drew Kasper: Do we have any other questions?

701
02:14:42.890 --> 02:14:43.480
Drew Kasper: Go ahead.

702
02:14:43.480 --> 02:14:50.529
Jasmine Dhindsa: Yes, this is Dr. Jasm Dunza, with Cms. In the slide. 4 of your presentation.

703

02:14:50.810 --> 02:14:55.739
Jasmine Dhindsa: You. It is stated that can you please go to slide 4

704
02:15:00.810 --> 02:15:05.510
Jasmine Dhindsa: or 92 in the overall deck.

705
02:15:06.980 --> 02:15:15.769
Drew Kasper: Brenda, do you mind looking for? I guess that would be for the 4th slide in we lose pagination with the consolidation of the deck.

706
02:15:15.930 --> 02:15:19.349
Drew Kasper: But, we should be able to figure this out.

707
02:15:22.590 --> 02:15:23.470
Jasmine Dhindsa: So.

708
02:15:25.160 --> 02:15:33.660
Jasmine Dhindsa: It states that you know the other regimens which cause excess, morbidity, and mortality due to liver bypass.

709
02:15:33.680 --> 02:15:55.709
Jasmine Dhindsa: and the study that was referred was by Bland 2022, which is an open label, prospective phase, 3. Study, and which measures actually 36 month event, free survival as well as overall survival. Can you please explain how that mechanistically explained the liver metabolism as the cause of effect.

710
02:15:56.160 --> 02:16:07.110
Mark Fosdal: Triosulphan is a pro drug to busolphan, so it bypasses liver metabolism and undergoes physiological metabolism under normal physiological conditions is the short answer.

711
02:16:09.290 --> 02:16:12.350
Mark Fosdal: Whereas Busolphan undergoes liver, metabolism.

712
02:16:14.580 --> 02:16:22.610
Jasmine Dhindsa: Okay, but that was not what was studied in that particular bill. In 42.

713

02:16:23.070 --> 02:16:24.230
Mark Fosdal: In that

714
02:16:24.520 --> 02:16:47.070
Mark Fosdal: in the Blin 2022. That's the final analysis that I was referring to looking at Truesulfin at 10 grams for 3 days, so total of 30 grams per meter squared to Flubu, 2 in the 570 patients. That was that large prospective study, looking at those that were Mac ineligible, or people that could not tolerate a myeloblative conditioning regimen.

715
02:16:48.270 --> 02:16:48.776
Mark Fosdal: Thank you.

716
02:16:57.879 --> 02:17:00.449
Drew Kasper: The questions from Cms. Or the public.

717
02:17:06.419 --> 02:17:11.179
Drew Kasper: no questions in the Q. And a. And no raised hands from attendees.

718
02:17:12.719 --> 02:17:18.329
Drew Kasper: We have no new questions in the new tech mailbox.

719
02:17:21.269 --> 02:17:23.039
Drew Kasper: Okay, last call for questions.

720
02:17:26.179 --> 02:17:32.609
Drew Kasper: Alright. Well, thank you for your presentation. And now we will.

721
02:17:33.089 --> 02:17:34.719
Drew Kasper: Oh, was someone trying to talk.

722
02:17:35.580 --> 02:17:36.990
Mark Fosdal: No, that's just me. Thank you.

723
02:17:38.160 --> 02:17:42.940
Drew Kasper: Thanks. And now we'll move into a break for lunch.

724
02:17:43.570 --> 02:17:48.060
Drew Kasper: and we will all meet back here at 12 pm.

725
02:17:48.600 --> 02:17:49.770
Drew Kasper: Thanks, everybody.

726
02:17:50.209 --> 02:17:55.389
Drew Kasper: You can leave your your terminal logged in and

727
02:17:55.580 --> 02:17:59.170
Drew Kasper: just mute it, and we'll turn back at 12. See you? Then

728
02:18:08.450 --> 02:18:23.569
Drew Kasper: we will be starting again in just a minute here, having come back from our lunch break. Just wanted to take a moment as a reminder that all attendees may submit their questions, using the Q. And a feature at the bottom of the screen.

729
02:18:23.780 --> 02:18:28.929
Drew Kasper: or you can use the raise hand feature in zoom, and we will be able to

730
02:18:29.219 --> 02:18:32.680
Drew Kasper: enable you to unmute and ask your question

731
02:18:33.320 --> 02:18:46.599
Drew Kasper: for those who are dialed in by telephone. You'd need to email your question to the Cms new tech email box at NEWT. ech@cms.hhs.gov

732
02:18:47.679 --> 02:19:02.620
Drew Kasper: for presenters who may have just joined for the latter half of the day here. I'd like to remind folks that we have allotted exactly 10 min for each presentation, after which we will be taking questions from the public and then from Cms

733
02:19:02.850 --> 02:19:20.689
Drew Kasper: with responses from presenters. That portion is estimated to be 5 min, but they run over may run less. We try to leave that room for QA. And we try to keep the presentations right to 10 min to keep

it equitable across presenters.

734
02:19:21.870 --> 02:19:29.509
Drew Kasper: Cms will be advancing the slides for each presentation and preventers should indicate when to advance to the next slide.

735
02:19:32.219 --> 02:19:34.800
Drew Kasper: and we are now

736
02:19:35.219 --> 02:19:45.369
Drew Kasper: back from lunch officially, so we'll now hear from presenters for tablet, and you may now unmute your phone and introduce yourself.

737
02:19:49.860 --> 02:20:10.200
Susan Prockop: Hi, I'm Susan Prokop, and I'm a pediatric transplant attending at Boston children's Santa Barbara, and I really appreciate the opportunity to speak to you today about treatment with Doubleuclazel for patients with Ebv driven post-transplant lymphoproliferative disease. Next slide, please.

738
02:20:12.530 --> 02:20:21.110
Susan Prockop: These are my disclosures relevant to my presentation today. Is my consultancy for tar value therapeutics and purifib next slide.

739
02:20:23.600 --> 02:20:44.369
Susan Prockop: So post-transplant, lymphoproliferative disease or Ptld is a potentially lethal complication of either hematopoietic stem cell or solid organ transplant, and the majority of cases of Ptld are Ebv driven. They result from either newly acquired or reactivated Ebd virus

740
02:20:44.500 --> 02:20:56.590
Susan Prockop: that primarily infects B lymphocytes and this disease emerges as a result of impaired Ebv directed immunity. In these immune compromised transplant recipients.

741
02:20:56.930 --> 02:21:16.640
Susan Prockop: There are currently no approved therapies for treatment of Vvv Ptld recommended treatment includes reduction of immune suppression, an approach which can increase the risk for graft versus

host disease and hematopoietic transplant recipients, and for organ rejection in solid organ transplant recipients.

742
02:21:17.430 --> 02:21:24.069
Susan Prockop: Additional treatment approaches include CD, 20, targeting monoclonal antibody therapies, such as rituximab

743
02:21:24.270 --> 02:21:37.619
Susan Prockop: and lymphoma directed chemotherapy. Although this latter approach is used rarely in hematopoietic transplant recipients and can be difficult to tolerate for medically fragile patients. Next slide please.

744
02:21:40.130 --> 02:22:06.570
Susan Prockop: In addition, and importantly, those patients with Ebvptld whose disease fails to respond to initial therapy experience, inferior outcomes and high mortality, and a shortened survival as demonstrated in these 2 multicenter retrospective studies on the left in the hematopoietic transplant setting. Those patients whose disease failed to respond to 1st line therapy with either Rituximab

745
02:22:06.600 --> 02:22:13.379
Susan Prockop: or Rituximab and chemotherapy experienced the median overall survival of just 0 point 7 months.

746
02:22:13.590 --> 02:22:32.690
Susan Prockop: and on the right a similar analysis in solid organ transplant recipients demonstrated a median overall survival for those failing to respond to 1st line therapy of just 4.1 months. This really demonstrates the high unmet need for these patients with refractory disease. Next slide, please.

747
02:22:34.850 --> 02:22:46.699
Susan Prockop: If approved, Tabalucasel will be the 1st FDA-approved therapeutic agent for patients with relapsed or refractory Ebvptld emerging after hematopoietic or solid organ transplant

748
02:22:47.060 --> 02:22:52.990
Susan Prockop: tabalucasel is an allogeneic off-the-shelf ebv specific t-cell immunotherapy

749
02:22:53.150 --> 02:23:08.689

Susan Prockop: and the product is not genetically modified, and it targets Ebv infected cells through the native T cell receptor depicted here in this slide with the Hla molecule representing Ebv. Epitopes presented by Hla

750
02:23:09.270 --> 02:23:12.660
Susan Prockop: Tabalucale is administered without lymphodepletion.

751
02:23:12.830 --> 02:23:20.210
Susan Prockop: It can be administered either inpatient or outpatient, and requires only 2 h of post-infusion monitoring

752
02:23:20.850 --> 02:23:24.729
Susan Prockop: and I'll talk about it. Safety profile in another slide.

753
02:23:24.990 --> 02:23:35.549
Susan Prockop: Taboocla received approval in Europe in 2022, and is under priority review with a Pdufa target action, date of January 15, th 2025.

754
02:23:35.660 --> 02:23:36.870
Susan Prockop: Next slide, please.

755
02:23:39.130 --> 02:23:48.639
Susan Prockop: So what is Tabuluclasel? Tabluclasel is a T-cell immunotherapy that's generated from normal healthy Ebv Seropositive donors

756
02:23:48.800 --> 02:23:56.410
Susan Prockop: the after leukophoresis the B cells are separated and transformed with a laboratory strain of the Epstein-barr virus.

757
02:23:56.630 --> 02:24:05.429
Susan Prockop: These transformed B cells serve as professional antigen presenting cells, and are co-cultured with T cells separated from the same leukophoresis.

758
02:24:05.930 --> 02:24:11.689
Susan Prockop: With this stimulation, T cells, recognizing ebb are sensitized and expanded.

759
02:24:12.060 --> 02:24:19.640
Susan Prockop: and when the culture is completed, the T cell lot is fully characterized and frozen for potential, immediate off-the-shelf use.

760
02:24:20.130 --> 02:24:31.200
Susan Prockop: and then each lot is selected for each patient based on sharing of the Hla allele through which the T cells recognize Ebv.

761
02:24:31.330 --> 02:24:41.729
Susan Prockop: so they're not fully Hla identical, such as a hematopoietic transplant donor would be but matched for how they recognize Ebv. Next slide, please.

762
02:24:43.690 --> 02:25:10.530
Susan Prockop: The efficacy and safety of Tabalucasel is being studied in the Allele trial. This is an ongoing global phase. 3 pivotal study in patients with either relapsed or refractory. Ebd. Ptld. The trial is open to recipients of hematopoietic transplant with Ptld that failed to respond to rituximab and to recipients of solid organ transplant with Ptld that has failed to respond to either Rituximab or Rituximab and chemotherapy.

763
02:25:11.090 --> 02:25:28.319
Susan Prockop: The treatment is administered in 35 day cycles with dosing of Tabalucasel at 2 million cells per kilo on days 1, 8 and 15, and response assessment around day 35, and the primary endpoint of objective response rate by Ioqr.

764
02:25:28.970 --> 02:25:48.580
Susan Prockop: Patients can receive multiple cycles of taboluka cell until they meet end of treatment. Criteria and subsequent cycles can be administered from the same lot for those responding to treatment, or potentially from a different lot that recognizes Ebv through a different age. Allele for those not responding.

765
02:25:48.700 --> 02:25:50.049
Susan Prockop: Next slide, please.

766
02:25:52.690 --> 02:26:09.180
Susan Prockop: Here we're presenting data from a subset of 43 patients

on the Allele trial, whose treatment aligns with the Us. Label. The Median age of this population was 42.3 years, but spans from less than 3 years of age to 75 years of age.

767
02:26:09.480 --> 02:26:14.829
Susan Prockop: 34 of these patients had an intermediate or high Ptld. Prognostic risk index.

768
02:26:14.960 --> 02:26:26.620
Susan Prockop: 32 of them had extranodal disease, and the majority had a histology consistent with diffuse large b-cell, lymphoma, very aggressive form of Ebv post-transplant lymphoproliferative disease.

769
02:26:27.160 --> 02:26:33.160
Susan Prockop: As you can see, the solid organ transplant cohort were recipients of a range of different organ transplanted

770
02:26:33.260 --> 02:26:34.730
Susan Prockop: next slide please.

771
02:26:37.290 --> 02:26:57.160
Susan Prockop: Here we're showing response rates in green. So 48% of the hematopoietic transplant recipients and 50% of the solid organ transplant recipients experienced responses in the Hct cohort, 28% achieved a complete and 20% partial response. And similarly.

772
02:26:57.160 --> 02:26:58.530
Catherine Bernstein: 3 min remaining.

773
02:26:59.620 --> 02:27:00.400
Susan Prockop: Sorry.

774
02:27:01.540 --> 02:27:03.209
Catherine Bernstein: You have 3 min remaining.

775
02:27:03.210 --> 02:27:10.079
Susan Prockop: Okay? Similarly, in the sot recipients, complete response was 22 and 28% next slide please.

776
02:27:11.930 --> 02:27:36.799

Susan Prockop: Most importantly, those patients who responded to therapy experience improved one year overall survival of 76.2% compared to those who did not respond who had a 1 year overall survival of just 24.7%. This survival benefit is in contrast to the predicted Median survival, 0 point 7 and 4.1 months. I showed previously. Next slide, please

777
02:27:38.230 --> 02:27:58.689
Susan Prockop: in terms of toxicity. 40 of these 43 medically complex patients had treatment, emergent adverse events. None of the fatal events were related to treatment with most common events being fever, nausea, and disease progression. There was one event of Gvhd and one of solid organ rejection, but neither were attributed to treatment.

778
02:27:58.860 --> 02:28:12.289
Susan Prockop: and this therapy is not associated with the toxicities of cytokine release, syndrome and neurologic toxicity commonly seen in the context of genetically modified car t cell therapy. Next slide, please.

779
02:28:14.300 --> 02:28:26.139
Susan Prockop: In summary. If approved, tabaluclazel will be the 1st FDA approved option for treatment of relapsed or refractory ebv-associated ptld emerging after hematopoietic or solid organ transplant

780
02:28:27.120 --> 02:28:43.799
Susan Prockop: clinical evidence augmented by real world post-marketing experience in the European setting establishes tableau cell as a transformative and off-the-shelf cell therapy for relapsed refractory Ebvptld, where survival is otherwise measured in weeks to months.

781
02:28:44.530 --> 02:29:05.159
Susan Prockop: These responses are clinically meaningful with rapid anti-tumor activity, a clear survival benefit and a favorable risk. Benefit profile. Tabaluca will address an urgent, unmet need in this medically complex, critically ill, patient population who remain immune, compromised.

782
02:29:05.450 --> 02:29:08.920
Susan Prockop: Thank you for your attention. I'm happy to take any questions.

783

02:29:11.160 --> 02:29:13.420
Drew Kasper: And thank you for your presentation.

784
02:29:13.940 --> 02:29:16.510
Drew Kasper: Now open up for questions from the public.

785
02:29:21.370 --> 02:29:24.829
Drew Kasper: We don't have any new questions in the new tech mailbox.

786
02:29:25.290 --> 02:29:29.419
Drew Kasper: I don't see any hands raised from attendees at this time.

787
02:29:30.470 --> 02:29:33.970
Drew Kasper: There are no new questions in the Q. And a.

788
02:29:35.000 --> 02:29:51.329
Drew Kasper: And so with that we'll open up more broadly. Public questions may still come in through the Q. And A. Or through raised hands, but we will now open up to questions from my colleagues at Cms. You can go ahead and unmute.

789
02:29:54.000 --> 02:29:57.809
Dorota Marchel: Hi, Hi, Dr. Prokup. This is Jordan Marshall, with Cms

790
02:29:58.381 --> 02:30:06.180
Dorota Marchel: in the clinically meaningful outcome slide. I think it was called it's slide one, number 1, 20, I think.

791
02:30:07.860 --> 02:30:16.880
Dorota Marchel: I noticed there was a large portion of the solid organ transplant population. It was 28% that fell into the not evaluable category.

792
02:30:17.356 --> 02:30:21.469
Dorota Marchel: So I was wondering what determines if a patient falls into that category.

793
02:30:22.280 --> 02:30:26.470
Susan Prockop: Sorry. I think this is the was the next slide. Not that one.

794
02:30:26.470 --> 02:30:28.809
Dorota Marchel: Yeah, I don't think it's this one. Yeah.

795
02:30:30.001 --> 02:30:38.232
Susan Prockop: So you know the for patients who? So it's not

796
02:30:39.740 --> 02:30:44.990
Susan Prockop: 20. So there I that was in the solid organ transplant setting. Yes, so

797
02:30:45.950 --> 02:31:05.170
Susan Prockop: that's determined. If they have gone off therapy or gotten alternative, therapy was the most was the most common, or had not completed the cycle. So if they didn't complete a cycle and had alternative therapy.

798
02:31:08.790 --> 02:31:10.130
Dorota Marchel: Okay, thank you.

799
02:31:12.690 --> 02:31:13.429
Dorota Marchel: No other questions.

800
02:31:13.430 --> 02:31:15.604
Susan Prockop: The other things that can

801
02:31:16.350 --> 02:31:21.648
Susan Prockop: that can make somebody not a valuable is if they've had

802
02:31:22.590 --> 02:31:27.180
Susan Prockop: like a surgery at the site of one of their sites of a valuable disease.

803
02:31:33.320 --> 02:31:34.059
Dorota Marchel: Thank you.

804
02:31:39.490 --> 02:31:42.669
Drew Kasper: We have any other questions from Cms or the public

805
02:31:48.530 --> 02:31:51.970
Drew Kasper: public could also include other presenters.

806
02:31:54.200 --> 02:31:57.609
Drew Kasper: Go ahead and unmute and chime in. If you have additional questions.

807
02:31:58.620 --> 02:32:02.190
Drew Kasper: Attendees raise hand or enter into the Q. And a.

808
02:32:03.580 --> 02:32:08.830
Drew Kasper: Don't see any raised hands at this time, or new Q. And a questions.

809
02:32:09.800 --> 02:32:13.650
Drew Kasper: and there are no new questions in the new tech mailbox.

810
02:32:14.140 --> 02:32:19.029
Drew Kasper: So with that, thank you for your presentation.

811
02:32:19.520 --> 02:32:25.829
Drew Kasper: and we will now move on to hear from presenters for Breyonzi.

812
02:32:26.860 --> 02:32:29.519
Drew Kasper: You may now unmute your phone and introduce yourself. Thanks.

813
02:32:32.060 --> 02:32:48.180
Peter Riedell: Good morning. My name is Dr. Peter Rydell, and I'll be presenting information regarding Breonzi or lysocaptogene Meralucil in the treatment of relapsed or refractory chronic, lymphocytic, leukemia, or small lymphocytic lymphoma, also known as Cll or Sll. Next slide. Please.

814
02:32:52.860 --> 02:32:59.310
Peter Riedell: Today I'll be speaking this is my disclosures. And relevant information. Next slide, please.

815

02:33:02.150 --> 02:33:21.789
Peter Riedell: Today I'll be speaking about Breonzi or Lysocel. Bryanzi is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia, or small lymphocytic lymphoma, who received at least 2 prior lines of therapy, including a Bruton tyrosine kinase inhibitor or Btki, and a b-cell lymphoma 2 inhibitor or Bcl. 2. Inhibitor

816
02:33:22.140 --> 02:33:36.609
Peter Riedell: of note. This indication is approved under accelerated approval, based on response rate and Median duration and duration, response and continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

817
02:33:36.750 --> 02:33:52.189
Peter Riedell: Notably there are no head-to-head comparisons of Breyonzi with existing therapies and we acknowledge the caveats inherent with cross-trial comparisons, due to differences in patient population. Baseline comorbidities, and the number and type of prior treatment subjects received next Slide please

818
02:33:53.850 --> 02:34:12.409
Peter Riedell: Cll is characterized by the progressive accumulation of dysfunctional mature B. Lymphocytes in the bone marrow, peripheral blood and lymphoid tissue and cll and sll are considered to have identical pathologic, and immunophenotypic features, wherein Cll manifests primarily in the blood, and Sll manifests primarily in the lymph, nodes.

819
02:34:12.700 --> 02:34:23.809
Peter Riedell: Cll is one of the most common hematologic malignancies with nearly 21,000 new cases each year in the United States. And it's also a disease of older patients with a Median age of diagnosis of 70 years.

820
02:34:24.260 --> 02:34:41.060
Peter Riedell: There is significant heterogeneity within Cll, and those with high-risk disease or cytogenetic features, including chromosome. 17. P deletion or tp. 53 mutations have a very poor prognosis, as do patients previously treated with Btk inhibitors and Bcl. 2 inhibitors next slide, please.

821
02:34:43.110 --> 02:35:03.500

Peter Riedell: There remains an unmet need for patients with relapsed refractory Cll or Sll and recent real world data has shown that patients with relapsed Cll have 4 outcomes to subsequent therapies. 2 common classes of treatment options for Cll are Btk inhibitors and Bcl. 2 inhibitors and patients who have been exposed to both of these types of therapies are considered double class exposed.

822
02:35:03.870 --> 02:35:28.589
Peter Riedell: Recent data demonstrate that patients with Cll and Sll that have been exposed to or have failed. Both Btk inhibitors and Bcl. 2 inhibitors have poor outcomes and specifically in double class exposed patients. The Median Pfs range from 3 to 15.4 months, and median overall survival range from 3.6 to 21.2 months, and for patients double refractory meaning that they had failed. Both therapies outcomes are even worse.

823
02:35:29.160 --> 02:35:47.750
Peter Riedell: Recent phase 1, 2. Clinical trial data of a double class exposed patients with refractory Cll. Or Sll. Treated with Pertebrutinib, a non-covalent Btki demonstrated a Median progression-free survival of 16.8 months. However, complete response rates were 0%. Next slide, please.

824
02:35:49.250 --> 02:36:12.820
Peter Riedell: Bryonzi is a CD 19, directly autologous car T. Immunotherapy, composed of individually formulated CD 8 and CD 4 car T cells administered as a 1-time treatment. It works by binding to CD 19, expressed on the cell surface of tumor and normal B cells. And through this binding leads to activation and proliferation of car T cells. Release of pro-inflammatory cytokines and the cytotoxic killing of target cells.

825
02:36:13.030 --> 02:36:26.159
Peter Riedell: Bryanzi is currently approved in the treatment of patients with relapsed refractory Cll. And Sll. Who have received at least 2 prior lines of therapy, including a Btk inhibitor and a Bcl. 2 inhibitor collectively known as double class exposed patients.

826
02:36:26.320 --> 02:36:43.579
Peter Riedell: Brianzi is given as a single dose, one-time infusion, consisting of 90 to 110 million car positive T. Cells manufactured a 1. 1 ratio of CD. 8 to CD 4 cells, and each component is supplied separately in one or more single dose vials. Next slide please

827

02:36:45.210 --> 02:36:51.380
Peter Riedell: approval for Brianzian relapse. Refractory Cll or Sll was based on the transcend Cll. 0 0 4. Trial

828
02:36:51.490 --> 02:37:02.969
Peter Riedell: in the full study. Patient population patients treated at 2 dose levels, including dose level one and 2. We had a Median age of 65 years and patients had a median of 5 prior lines of therapy.

829
02:37:03.130 --> 02:37:15.459
Peter Riedell: 45% of patients had bulky lymph nodes and 83% of patients had high risk. Cytogenetic features, including 17 p. Deletion, Tp. 53. Mutation unmutated Ighv or complex cytogenetics.

830
02:37:15.730 --> 02:37:28.969
Peter Riedell: In the full study population, 100% of patients were Btki exposed with 88% Btki refractory, while 81% were Bcl. 2 inhibitor exposed and 76% were Bcl. 2 inhibitor refractory.

831
02:37:29.170 --> 02:37:40.760
Peter Riedell: notably baseline characteristics of the subset of 71 patients considered double refractory to both Btki and Bcl. 2 inhibitors were similar to the full study population. Next slide, please.

832
02:37:42.820 --> 02:37:50.010
Peter Riedell: The primary endpoint of the transcend Cll 0 0 4 study was complete response or complete response with incomplete hematopoietic recovery

833
02:37:50.130 --> 02:38:16.120
Peter Riedell: per the Iwcll 2018 criteria, as assessed by the Independent Review Committee or Irc. And here we see data for both the full study population and the double refractory subset. In this study we see that 19% of the full study population achieved a Cr or Cri and the Irc assessed overall response rate. For this population was 48% with a Median time to 1st response of 1.3 months and a Median time to 1st Cr or Cri of 5.5 months.

834
02:38:16.360 --> 02:38:29.570
Peter Riedell: In the double refactory subset, 20% of patients achieved a Cr or Cri with an overall response rate of 44% with a Median time to 1st response of 1.1 months and a Median time to 1st Cr

or cri of 2.1 months.

835
02:38:29.970 --> 02:38:41.690
Peter Riedell: In this study undetectable mineral residual disease, or Mrd was assessed by next generation, sequencing at any time, point, postcard, t cell infusion with a sensitivity of one times 10 to the minus 4

836
02:38:41.930 --> 02:38:49.259
Peter Riedell: 60% of patients achieved undetectable Mrd in the bone marrow. In both the full study population and in the double refractory subset.

837
02:38:49.640 --> 02:38:56.930
Peter Riedell: And thus Brianzi demonstrated deep and substantially improved clinical outcomes in patients with double class exposed, relapsed refractory cll

838
02:38:57.140 --> 02:38:58.529
Peter Riedell: next slide, please.

839
02:39:00.660 --> 02:39:02.469
Peter Riedell: Next slide, please.

840
02:39:04.890 --> 02:39:33.059
Peter Riedell: Additional data from the transcend. Cll 0 0 4 study was available at approximately 2 years follow-up, and for the subset of patients who had responded to Bryanzi. On the left we see data on 88 patients in the full study population who received Bryanzi at Dose Level 2 separated by response status, and patients who responded to Brianzi with a complete or partial response, had a Median duration of response of just over 35 months, and the Median duration of response was not reached for patients achieving a Cr or Cri.

841
02:39:33.410 --> 02:39:41.419
Peter Riedell: We see similar findings in patients who had progressed on Btk inhibitors and failed. Bcl. 2 inhibitors as delineated on the right, Kapenmeier curve

842
02:39:41.760 --> 02:39:50.720
Peter Riedell: for patients with relapse, refractory Cll and Sll treated with Brianzi, achieving a cr or Cri led to durable response,

and a median of 2 years follow-up next slide, please.

843
02:39:51.710 --> 02:40:18.040
Peter Riedell: Durable clinical benefit was also seen in terms of progression-free survival, and again we see the Pfs plot for the full population on the left, separated by response status, and those responding to Breyonce had more favorable progression-free survival than non-responders, which was also true. In those Btpi progressed Venetoclax failure subset at a meeting of 2 years follow-up. The Pfs. Was not reached for double class exposed patients who achieved a Cr or Cri with Brianzi. Next slide, please.

844
02:40:18.970 --> 02:40:40.349
Peter Riedell: Similarly, with overall survival, we see the separated by response status, and we see that patients who responded to Bryanzi with a Cr. Or Pr. Had more favorable overall survival than non-responders, and this was similarly true for the Btk progressive endetoclax failure subset collectively bryonzi demonstrated durable clinical benefit by showing improved overall survival in responders. Next slide, please

845
02:40:41.270 --> 02:41:03.299
Peter Riedell: the transcend. Cll. 0 4. Study demonstrated that Brianzi had a well-established safety profile, and we see here common. Any grade treatment, emergent adverse events included Cytokine release syndrome, followed by hematologic toxicity and the most common grade. 3 or greater treatment. Emergent adverse events were cytopenias overall. These safety data remained consistent with previous reports for Brionsi. Next slide please

846
02:41:04.690 --> 02:41:12.909
Peter Riedell: 85% of patients experience, Cytokine, release syndrome, mostly grade, one to 2 with a Median time to onset of 4 days and a Median time to resolution of 6 days.

847
02:41:12.910 --> 02:41:37.179
Peter Riedell: 45% of patients experienced neurologic events mostly grade one to 3, with both immediate time to onset, and a Median duration of 7 days. Approximately 70% required tocilizumab and or corticosteroids for the management of Crs or neurologic toxicity. And we saw other adverse events of special interest, including prolonged cytopenias in 54% grade, 3 or higher infections in 18% and hypoglymoglobulinemia in 15%.

848

02:41:37.880 --> 02:41:39.370
Peter Riedell: 5 deaths related to.

849
02:41:39.370 --> 02:41:40.570
Catherine Bernstein: You have 1 min remaining.

850
02:41:40.570 --> 02:41:56.750
Peter Riedell: Events were reported, including 4 considered unrelated to lysocel and one patient, experienced grade, 5. Macrophage activation syndrome considered related to lysocel. Collectively, these data are consistent with the well-established safety profile of Brionsi. Next slide, please.

851
02:41:58.290 --> 02:42:11.009
Peter Riedell: In summary. Brianzi is the 1st and only car t cell therapy specifically approved for the treatment of relapsed refractory double class exposed Cll and Sll. It satisfies the unmet need for therapies that can induce deep and durable responses in patients

852
02:42:11.220 --> 02:42:21.160
Peter Riedell: relapsed refractory Cll and Sll. Double class exposed patients experience poor outcomes with existing therapies and brionsi substantially improves clinical outcomes for these patients.

853
02:42:21.390 --> 02:42:31.870
Peter Riedell: Brianzi has shown deep and durable responses in relapsed refractory Cll, wherein we see 20% of patients achieving a Cr and responders showed extended progression-free and overall survival.

854
02:42:32.100 --> 02:42:41.169
Peter Riedell: And we feel that these outcomes are especially significant. Given Brianzi's well-established safety profile, and that the fact that it is a 1-time infusion rather than continuous treatment

855
02:42:41.540 --> 02:42:43.010
Peter Riedell: next slide, please.

856
02:42:44.130 --> 02:42:48.290
Peter Riedell: and with that I'd like to thank you for your time and attention. I'd be happy to take any questions.

857

02:42:52.510 --> 02:42:59.050
Drew Kasper: And thank you for your presentation. We'll open it up now for questions from the public.

858
02:43:03.840 --> 02:43:09.680
Drew Kasper: We don't yet have any questions in the QA. From the public or from raised hands

859
02:43:10.540 --> 02:43:13.580
Drew Kasper: in the attendees group.

860
02:43:16.380 --> 02:43:28.840
Drew Kasper: Don't have any raised hands with other panelists as well. So with that we'll move on to Cms questions. If anyone from the public does have a question, it's not too late to enter it in the Q. And a. Or to raise your hand.

861
02:43:29.010 --> 02:43:35.860
Drew Kasper: but we'll open it up to questions for my from my colleagues at Cms. You can go ahead and unmute now.

862
02:43:36.590 --> 02:44:00.209
Ron Kline: Yeah. Good afternoon. My name is Ron Klein. I'm a medical officer at Cms. 2 questions. First, st in the Lancet paper there were 9 responses, 18 complete response, 70 patients. And then the ash slides and the slides you just showed. Now, there's an additional complete responder and 71 patients. Can you speak to that additional patient, and how they wound up on study.

863
02:44:02.003 --> 02:44:12.360
Peter Riedell: They. I really appreciate you raising that question. Unfortunately, at top of mind, I don't have those details, but we'll certainly be happy to include that, with our supplemental comments.

864
02:44:12.360 --> 02:44:18.187
Ron Kline: Okay, great and and I guess the second. The second question is,

865
02:44:18.730 --> 02:44:21.420
Ron Kline: sort of a comparison of of

866

02:44:21.620 --> 02:44:36.890
Ron Kline: unmeasurable minimal residual disease and complete response. So just trying to look at the different criteria, it sounds like like minimal residual disease is based on blood and marrow and complete response might be based on nodal response as well is, that is that accurate.

867
02:44:37.070 --> 02:44:47.520
Peter Riedell: Yes, so the the responses in this study were assessed per Iwcll criteria, which is both based on nodal response along with hematopoietic recovery.

868
02:44:48.320 --> 02:44:59.609
Ron Kline: So it sounds like there was a subset of patients who had, I guess, a measurable Mrd, based on marrow and blood, but who still had nodal disease. But those patients

869
02:44:59.720 --> 02:45:10.940
Ron Kline: still did very well. So can you sort of speak to the issue of of you know whether complete response you know how you should think about this as Mrd versus nodal response.

870
02:45:10.940 --> 02:45:37.449
Peter Riedell: Absolutely. It's a great question, one that's come up often. So you know, with Cll, we often see that patients may harbor bulky lymph nodes, and even with treatment we may see resolution of a lot of their nodal burden, but it might not completely resolve to less than one and a half centimeters which would still qualify it as a partial response or not a complete response. However, there might not be evidence of residual disease based on blood or marrow in those patients.

871
02:45:37.810 --> 02:45:59.690
Ron Kline: I just want to. I'm a pediatric oncologist. So you sort of this Mrd question sort of got me interested in a lot of lymphomas like Hodgkin's disease. You still have large, large lymph nodes, but there's no active disease. They're sort of scarred scarring. Do you think the same thing is going on in Cll with the nodes that aren't responding in a setting of Mrd negativity.

872
02:46:00.048 --> 02:46:02.559
Peter Riedell: Yes, that I believe that's 1 explanation.

873

02:46:02.830 --> 02:46:04.210
Ron Kline: Absolutely right.

874
02:46:04.210 --> 02:46:06.350
Ron Kline: Okay, thank you very much. On to next person.

875
02:46:09.010 --> 02:46:13.546
Adina Hersko: Thank you. I'm Adina from Cms as well.

876
02:46:14.430 --> 02:46:25.490
Adina Hersko: talked about the complete response. But I'm curious. Can you talk a little bit about how the overall response rate the Pfs. Compared to existing therapies for Cll and Sll.

877
02:46:26.330 --> 02:46:50.240
Peter Riedell: Absolutely so in terms of the overall response rates for this agent, as I've mentioned in previous slides, was 48% for the entire population and 44% for those patients in the double refractory subset. There is overall limited data in the real world of using other agents in the post, Btki Post, Bcl. 2 setting.

878
02:46:50.300 --> 02:47:12.539
Peter Riedell: And, as I mentioned earlier, the real world data would suggest that outcomes are very poor for this subset. We do have one other FDA approved therapy that is indicated for patients that have progressed or exposed to those therapies which is perutinib. But as I mentioned, the cr rates in those population within that trial was 0%.

879
02:47:12.840 --> 02:47:36.569
Peter Riedell: And so we think that these results compare very favorably. And I think the other really impactful part of this therapy is that these responses do appear durable for those patients that achieve a Cr and even those patients responding have favorable long-term outcomes compared to what we've seen with some of the other or one of the other agents, that is, FDA approved at this point.

880
02:47:37.410 --> 02:47:47.560
Adina Hersko: Thank you. Can you talk a little bit about the Cr versus Cri endpoint? How many patients had just the complete response versus the Cri.

881
02:47:48.430 --> 02:47:49.150

Peter Riedell: But sure.

882
02:47:49.150 --> 02:47:54.000
Adina Hersko: Compared to other trials that may not have included kind of those 2 pieces and their endpoints.

883
02:47:54.240 --> 02:48:04.819
Peter Riedell: And and just so, I'm clear you're you're breaking you wanting a breakdown between those achieving a cr versus cr with incomplete, hematic recovery. What's the breakdown of those individualized.

884
02:48:04.820 --> 02:48:06.710
Adina Hersko: Yeah, I was just curious about that.

885
02:48:06.710 --> 02:48:15.209
Peter Riedell: Okay. That's a great question. I actually also don't have that information at top of mind. But we can certainly provide that in the supplemental comments.

886
02:48:15.600 --> 02:48:27.509
Adina Hersko: Thank you. And just one last question, when looking at the treatment, emergent adverse events for Brianzi and other treatments approved for Cll. Sll, how do you look at those and compare those.

887
02:48:28.150 --> 02:48:53.139
Peter Riedell: Yeah. So you know, we're seeing in the context of this treatment, Cytokine, release syndrome, which is, of course, a more unique toxicity to cellular therapies. And so that's not a toxicity. We would anticipate seeing with other targeted agents, although I would argue that overall that was well managed in this study, and we only saw 8% of patients having grade 3 or greater events. Other common toxicities with cellular therapy

888
02:48:53.140 --> 02:49:03.900
Peter Riedell: include hematologic toxicity, which is also inherent with other targeted agents, and you know that was also managed with supportive care measures in the context of this trial.

889
02:49:04.243 --> 02:49:12.486
Peter Riedell: I think you know, these are obviously different

therapies that are associated with different side effect. Profiles. However, you know, I think with

890
02:49:12.830 --> 02:49:20.649
Peter Riedell: proper management, these these toxicities can, you know, easily be managed for for patients undergoing this treatment.

891
02:49:21.820 --> 02:49:24.030
Adina Hersko: Thank you. No more questions for me.

892
02:49:29.520 --> 02:49:32.629
Drew Kasper: Are there any other questions from Cms or the public?

893
02:49:36.730 --> 02:49:39.080
Drew Kasper: There are no new questions in the Q. And A.

894
02:49:39.580 --> 02:49:45.819
Drew Kasper: There are no raised hands, and there are no new questions in the new tech mailbox.

895
02:49:46.180 --> 02:49:49.049
Drew Kasper: So with that thanks again for your presentation.

896
02:49:49.480 --> 02:49:55.499
Drew Kasper: And we will now move on to hear from presenters for Cobenfi.

897
02:49:55.860 --> 02:49:59.310
Drew Kasper: You may now unmute your phone and introduce yourself.

898
02:49:59.770 --> 02:50:06.580
Ken Kramer: Good afternoon. My name is Ken Kramer, and I am. The medical affairs lead for neuropsychiatry at Bms. We can go to

899
02:50:06.910 --> 02:50:08.340
Ken Kramer: the next slide, please.

900
02:50:08.540 --> 02:50:27.030
Ken Kramer: These are my relevant disclosures, and I would like to

thank you for allowing me to represent my colleagues at Bms. And to present on Cobenfy, zenomaline and trospium chloride for the treatment of adults with schizophrenia, which represents the 1st innovation in the treatment of schizophrenia in decades. Next slide, please.

901
02:50:27.720 --> 02:50:30.809
Ken Kramer: Here's what I'd like to cover in the next few minutes.

902
02:50:31.470 --> 02:50:32.970
Ken Kramer: Next slide. Please

903
02:50:33.750 --> 02:50:41.609
Ken Kramer: allow me to present some important context to level. Set us. Co. Benfi is approved by the FDA for the treatment of schizophrenia in adults.

904
02:50:41.970 --> 02:50:56.669
Ken Kramer: Cobenvi combines xenomaline, a dual m. 1 m. 4. Preferring muscarinic receptor, agonist and trospium, chloride a muscarinic receptor antagonist that does not appreciably cross the blood-brain barrier primarily acting in peripheral tissues to enhance tolerability.

905
02:50:56.910 --> 02:51:04.299
Ken Kramer: while the exact mechanism of action of Co. Benfi is unknown. Its efficacy is thought to be due to the agonist activity

906
02:51:04.530 --> 02:51:09.719
Ken Kramer: of Xenomaline at m. 1 and M. 4. Muscarinic receptors in the central nervous system.

907
02:51:10.220 --> 02:51:20.539
Ken Kramer: For nearly 70 years schizophrenia has been treated with essentially a single class of medication that all share a common mechanism of action, dopamine, receptor, binding, and antagonism.

908
02:51:20.840 --> 02:51:29.600
Ken Kramer: Cobenfy's unique mechanism of action involves modulating several neurotransmitters through agonism of the m. 1 and M. 4. Muscarinic receptors.

909

02:51:29.890 --> 02:51:47.610
Ken Kramer: Unlike traditional antipsychotics that primarily target dopamine receptors co benfi's approach reduces the likelihood of side effects like weight gain, metabolic dysfunction, sedation, and motor disturbances which can be challenging in long-term schizophrenia management and may ultimately improve adherence to treatment.

910
02:51:48.010 --> 02:52:00.689
Ken Kramer: There is no head-to-head comparison of cobantry with existing therapies, and we acknowledge the caveats inherent with indirect cross-study comparisons, due to differences between patient populations, baseline symptomatology.

911
02:52:00.920 --> 02:52:07.520
Ken Kramer: and the number and type of prior treatment regimens that subjects have received previously. Next slide. Please

912
02:52:08.610 --> 02:52:15.329
Ken Kramer: like to talk a little bit about some facts and figures about schizophrenia. But I'd like to concentrate on the 4th one down.

913
02:52:15.570 --> 02:52:41.189
Ken Kramer: The estimated potential life lost in patients living with schizophrenia is about 30 years compared to the general population, and this is partially attributed to the disease itself and cardiovascular and metabolic comorbidities and an increased suicide rate. But it is not simply due to the disease, but can also be attributed to the current medications used to treat schizophrenia which carry substantial risk for weight, gain, and metabolic dysfunction.

914
02:52:41.510 --> 02:52:42.889
Ken Kramer: Next slide, please.

915
02:52:44.070 --> 02:53:00.320
Ken Kramer: Like many psychiatric illnesses, there has been a call for decades, for newer medications. As schizophrenia is essentially treated with a single class of medications. The unmet needs that have the most room for improvement are in efficacy, safety, and the ability for patients to stay adherent to their medication.

916
02:53:00.590 --> 02:53:17.700
Ken Kramer: The shortcomings of the current standard of care leads to

3 out of 4 patients. Discontinuing therapy after the 1st 18 months, and discontinuations can lead to relapse and relapse often leads to hospitalization, incarceration, and death in this very vulnerable population.

917
02:53:18.260 --> 02:53:19.870
Ken Kramer: Next slide, please

918
02:53:20.520 --> 02:53:39.100
Ken Kramer: allow me to speak to what makes Copenfi different from the current standard of care in schizophrenia. As I stated before, muscarinic receptors are expressed in brain regions implicated in psychosis and cognition, suggesting that their modulation can treat the overall symptoms of schizophrenia.

919
02:53:39.670 --> 02:53:51.479
Ken Kramer: Cobenfy does not directly modulates dopamine or serotonin receptors, and this provides a clear rationale for the lack of dopamine and serotonin related side effects that we will see in subsequent slides

920
02:53:51.680 --> 02:54:01.689
Ken Kramer: the unique pharmacology of Cobenfy enables its differentiated efficacy and safety profile as seen across multiple positive clinical trials. Next slide, please.

921
02:54:02.650 --> 02:54:09.579
Ken Kramer: Here's the study design shared by the 3 five-week pivotal studies for Cobenfi, known as Emergence 1, 2, and 3.

922
02:54:09.720 --> 02:54:31.990
Ken Kramer: These were double-blind, placebo-controlled studies of 5 weeks duration in hospitalized adult patients with schizophrenia who were experiencing an acute exacerbation of psychosis. All patients in the experimental group were titrated to the highest Cobenvi dose of 1, 25, over 30 milligrams bid where the 1st number signifies the dose of Xenomaline, which is the target compound.

923
02:54:32.420 --> 02:54:44.490
Ken Kramer: Select eligibility, criteria are shown on the slide and the primary efficacy. Endpoint was the change from baseline in the positive and negative syndrome scale or pans. Total score at week. 5

924
02:54:44.830 --> 02:54:46.180
Ken Kramer: next slide, please.

925
02:54:47.060 --> 02:55:09.009
Ken Kramer: This is our data for our primary efficacy. Endpoint the change from baseline and pans. Total score the response to 125 over 30 milligrams of Co. Benfi was statistically significant and clinically relevant for total schizophrenia symptoms across 3 emergent trials. All 3 studies showed at least an 8 point reduction from placebo.

926
02:55:09.360 --> 02:55:16.010
Ken Kramer: A statistically significant split from Placebo was seen as early as week 2, and was sustained through week 5.

927
02:55:16.440 --> 02:55:31.469
Ken Kramer: The effect sizes for Cobanfi were considerably higher than what has been published for older treatments. This comes from indirect treatment. Comparisons that show that most treatments have effect sizes somewhere between 0 point 3 and 0 point 4 5,

928
02:55:31.720 --> 02:55:38.180
Ken Kramer: and effect size is a measure of how well the experimental group does in comparison to its own placebo group.

929
02:55:38.760 --> 02:55:40.210
Ken Kramer: Next slide, please.

930
02:55:43.010 --> 02:56:03.210
Ken Kramer: turning to positive symptoms which are one of the 3 key symptom types. This effect was statistically significant and clinically relevant for positive symptoms which include hallucinations and delusions in all 3 emergent trials as measured by the pans, positive subscale score, and averaged about a 3 point difference from placebo

931
02:56:03.650 --> 02:56:05.020
Ken Kramer: next slide, please.

932
02:56:06.470 --> 02:56:25.580
Ken Kramer: The tolerability of Co. Benfi is as remarkable for the adverse events that we observed for as much as those that we did not

observe. We saw mainly pro-cholinergic and Anticholinergic adverse events. Many of them gi related that were mild to moderate in severity and transient in duration with repeated dosing.

933
02:56:25.630 --> 02:56:39.780
Ken Kramer: What we did not see in any significant incidents were the aes typically associated with the old standard of care, such as weight, gain, sedation, and motor abnormalities, all which are historically associated with discontinuation in the real world setting

934
02:56:40.040 --> 02:56:54.680
Ken Kramer: based on this unique tolerability profile. The Uspi of Cobenfi does not have atypical antipsychotic class warnings and precautions, and does not have a boxed warning for increased mortality in elderly patients with dementia-related psychosis.

935
02:56:55.030 --> 02:56:56.480
Ken Kramer: Next slide, please.

936
02:56:58.330 --> 02:57:09.119
Ken Kramer: When we begin to the discussion of what the substantial clinical impact of Cobenfi is, we turn to the impact on negative symptoms, such as abolition, anasagnosia. So you have 3.

937
02:57:09.120 --> 02:57:09.820
Catherine Bernstein: It's remaining.

938
02:57:09.820 --> 02:57:26.809
Ken Kramer: Social withdrawal and anhedonia, which are among the most difficult to treat with dopamine receptor antagonists. Cobenfe is an effective treatment option for patients experiencing disruptive negative symptoms due to its distinct mechanism of action as opposed to traditional d. 2 blocking agents

939
02:57:27.410 --> 02:57:44.509
Ken Kramer: across 2 of the 3 emergent trials there was a statistically significant improvement in negative symptoms, as demonstrated with the pans negative subscale score in emergent 3 we observed a statistical significance at week 4. But this was unexpectedly lost at week. 5. Next slide, please.

940
02:57:44.930 --> 02:58:09.250

Ken Kramer: These are the safety and tolerability tables from emergent 2 and 3. It is clear that the most common Aes are pro and Anticholinergic in nature. What is not seen in these tables are motor abnormalities, sedation, and other adverse events. The most impressive result, though, is on weight change over 5 weeks of treatment. Weight, change was essentially placebo-like and small in magnitude, and nearly twice as many placebo treated subjects gained

941
02:58:09.380 --> 02:58:20.440
Ken Kramer: potentially, clinically significant body weight. Compared to Co. Benfi, treated subjects, changes in objective. Motor scales were placebo-like as well as demonstrating no change in motor symptoms

942
02:58:20.540 --> 02:58:23.489
Ken Kramer: which is inclusive of Eps and Akathisia.

943
02:58:23.610 --> 02:58:24.959
Ken Kramer: Next slide, please.

944
02:58:25.390 --> 02:58:50.739
Ken Kramer: However, we know that schizophrenia is a lifelong illness, requiring prolonged treatment in emergent 4, which was an open label extension of emergent 2 and 3. You can see on the upper right that the treatment effect of Co. Benfi continued, and was maintained over 52 weeks with no sign of tachaphylaxis. Looking at the pooled safety analysis of these 2 52 week open label safety studies. There were no new safety signals observed.

945
02:58:50.940 --> 02:58:57.589
Ken Kramer: and Aes remain mostly mild, to moderate in severity and transient in duration with continued treatment.

946
02:58:57.800 --> 02:58:59.269
Ken Kramer: Next slide, please.

947
02:58:59.800 --> 02:59:08.329
Ken Kramer: Quickly returning to the acute studies when looking at the severity of illness, using the Cgis. All 3 emergent studies show statistically significant.

948
02:59:08.330 --> 02:59:08.680
Catherine Bernstein: 1 min.

949
02:59:08.680 --> 02:59:15.660
Ken Kramer: Improvements in the Hcp's perception of how severe patient symptoms were at 5 weeks.

950
02:59:16.250 --> 02:59:42.730
Ken Kramer: and finally, next slide, please to summarize. Co. Benfi is the 1st new treatment for schizophrenia in nearly 70 years, based on a 1st in class Moa of m. 1 and M. 4. Muscarinic receptor agonism that does not bind to nor block dopamine. D. 2 receptors, as all other current treatments do. To some extent we believe that the novel Moa drives the efficacy and differentiated safety profile of Co. Benfi, both which are needed to improve the lives of patients

951
02:59:42.740 --> 02:59:47.629
Ken Kramer: currently living with schizophrenia, which is the true value of Co. Benfi is in both.

952
02:59:48.080 --> 03:00:12.100
Ken Kramer: Cobenfe has shown strong and durable efficacy and safety profile that supports its long-term use, and we hope that we have adequately demonstrated why Co. Benfi should be considered the 1st substantial advancement in the treatment of schizophrenia in a very long time to help persons living with this terrible illness have an opportunity to lead their best lives, and with that I thank you, and I'm happy to take any of your questions.

953
03:00:15.720 --> 03:00:19.719
Drew Kasper: Thank you for your presentation. We'll open up for questions from the public first.st

954
03:00:24.860 --> 03:00:28.499
Drew Kasper: I don't see any questions in the Q. And A.

955
03:00:29.860 --> 03:00:32.940
Drew Kasper: And I don't see any raised hands

956
03:00:34.200 --> 03:00:42.099
Drew Kasper: as a reminder for the public. That's how we would know that you have a question is through entering the Q. And a or a raised hand.

957
03:00:42.340 --> 03:00:45.250
Drew Kasper: and after which we could unmute you.

958
03:00:45.980 --> 03:00:47.960
Drew Kasper: So with that

959
03:00:48.420 --> 03:01:06.639
Drew Kasper: there are no questions in the new tech mailbox. Either we will move on to questions from Cms. If anyone has a question from the public, feel free to enter it in the Q. And a. Or raise a hand, but we'll move on also to open it up to questions from my colleagues at Cms. Please go ahead and unmute.

960
03:01:08.770 --> 03:01:13.709
Dorota Marchel: Hi, Dr. Kramer, thank you for that. This is Dorotta Marshall, with Cms

961
03:01:14.753 --> 03:01:25.836
Dorota Marchel: so in the slide where we were looking at the longer term outcomes. It was slide 1 55, I think, in the

962
03:01:27.000 --> 03:01:33.000
Dorota Marchel: in the presentation. Yeah, the one after that, this one. Yeah.

963
03:01:33.608 --> 03:01:49.090
Dorota Marchel: So it appears that the difference between Coben Fee and the placebo group in terms of change in the baseline pants total score was greatest at 5 weeks, and then over the longer term, follow up. It looked a bit more similar.

964
03:01:49.450 --> 03:01:58.620
Dorota Marchel: And that's the graph in the top right is there? Statistically significant degree of improvement for those treated with Copenfi compared to Placebo in the long term.

965
03:01:59.300 --> 03:02:25.490
Ken Kramer: In the long term. What we saw after 5 weeks was 2 things, number one, that the placebo group caught up to the Co. Benfi group from Emergen 2 and 3 quite rapidly, and there was a continued improvement in Pan's total score over the 52 weeks. As this was a open

label extension primarily for efficacy, for I'm sorry for tolerability and safety. We don't have any statistical significance. At 52 weeks

966
03:02:26.400 --> 03:02:29.100
Ken Kramer: we report this. The descriptive statistics.

967
03:02:29.380 --> 03:02:30.020
Dorota Marchel: Okay?

968
03:02:30.510 --> 03:02:49.130
Dorota Marchel: And then you mentioned earlier in the presentation that for other treatments for schizophrenia there's a point 3 to 0 point 4 5 effect size historically, and I was just wondering where that information came from.

969
03:02:49.714 --> 03:02:52.359
Ken Kramer: That came from a meta analysis from Stefan Lucht.

970
03:02:54.350 --> 03:02:54.950
Dorota Marchel: Okay.

971
03:02:54.950 --> 03:03:06.020
Ken Kramer: And historically, the literature shows anywhere between 0 point 3 0 point 4 5 to 5. The highest is in clozapine, but that is indicated for treatment, resistant schizophrenia.

972
03:03:06.450 --> 03:03:07.100
Dorota Marchel: Okay,

973
03:03:09.360 --> 03:03:14.799
Dorota Marchel: And then I'm curious. Do you have an estimated timeframe? For when the results of the long term study will be published.

974
03:03:15.732 --> 03:03:18.949
Ken Kramer: Yes, those are currently being prepared for publication, as we speak.

975
03:03:19.260 --> 03:03:20.779
Dorota Marchel: Okay. Thank you.

976
03:03:20.780 --> 03:03:21.780
Ken Kramer: Quite welcome.

977
03:03:26.060 --> 03:03:50.780
Adina Hersko: Hi, this is Adina. From Cms. I had a question about the scoring with the pants scoring in the slide where you talked about the negative symptoms being improved, and how they were significant only in 2 out of the 3 trials, and then some of the other trials. It was a 1 point improvement. Can you talk about the clinical significance of a 1 point improvement in the pants, scoring.

978
03:03:51.790 --> 03:04:11.960
Ken Kramer: So if you, if you go back to the pans, total score, what's considered to be clinically significant is anything at or greater than 15 points from baseline, and, as you can see from the slide on pants, total score the Co. Benfi group in emergence 1, 2, and 3, all hit all hit that level

979
03:04:12.590 --> 03:04:19.300
Ken Kramer: pans. Positive score and the pans negative score are subscales and post hoc analyses from

980
03:04:19.420 --> 03:04:35.110
Ken Kramer: from the pans. Total score. But, unlike the pans total score. There's no real well accepted. What would be clinically significant for either the positive or negative subscale scores as much. It varies by opinion.

981
03:04:36.420 --> 03:04:37.690
Adina Hersko: Got it. Thank you.

982
03:04:37.690 --> 03:04:38.450
Ken Kramer: You're welcome.

983
03:04:41.540 --> 03:04:54.520
Adina Hersko: One other question you had talked about in real world patients on other treatments don't have good medication, adherence. How do you compare that to Co. Benfi, which was just tested for the 5 weeks.

984

03:04:55.374 --> 03:04:58.501
Ken Kramer: It's an excellent question. So, as you, as as you know,

985
03:04:59.240 --> 03:05:13.140
Ken Kramer: we were just approved by the FDA on September 26, th 2024, and we are currently opening up a real world evidence registry that will provide that information. It'll just take some time, of course.

986
03:05:13.810 --> 03:05:14.670
Adina Hersko: Thank you.

987
03:05:14.670 --> 03:05:15.700
Ken Kramer: You're quite welcome.

988
03:05:20.330 --> 03:05:23.300
Drew Kasper: There any other questions from Cms. Or the public?

989
03:05:27.010 --> 03:05:30.160
Drew Kasper: You have no new questions in the Q. And a.

990
03:05:31.290 --> 03:05:38.310
Drew Kasper: Or the Ntap mailbox, and we don't have any raised hands. Okay.

991
03:05:38.990 --> 03:05:44.060
Drew Kasper: so with that, thanks again for your presentation, and we will

992
03:05:45.150 --> 03:05:52.170
Drew Kasper: now move on to hear from presenters for, say, hierara

993
03:05:53.358 --> 03:05:57.300
Drew Kasper: you may now unmute your phone and introduce yourself.

994
03:05:59.240 --> 03:06:00.320
TELEPHONE_USER: Nick, can you hear me?

995
03:06:01.330 --> 03:06:02.689
Drew Kasper: We can. Thanks.

996
03:06:04.230 --> 03:06:18.009
TELEPHONE_USER: Great. My name is Katie Kelly, and I'm a professor of clinical medicine at Ucsf. In San Francisco, and I'm delighted to present on behalf of Jazz. The data and presentation for Xamidatumab for treatment of adults with previously treated

997
03:06:18.780 --> 03:06:26.609
TELEPHONE_USER: or metastatic her 2 positive by immunohistochemistry, 3 plus designation biliary tract cancers next slide, please.

998
03:06:30.730 --> 03:06:33.820
TELEPHONE_USER: Here my disclosures next slide.

999
03:06:38.160 --> 03:06:57.590
TELEPHONE_USER: The biliary tract cancers or Btc are a relatively rare cancer. But on the rise worldwide, particularly for intrapadic Cholangiocarcinomas. You can see on the schema on the left that these are anatomically quite complex cancers, including cancers of the bile, duct within the liver at the junction of the bile duct within the liver to the common hepatic duct

1000
03:06:57.590 --> 03:07:09.180
TELEPHONE_USER: and common bile duct, more distally termed as extrahepatic cholangiocarcinoma, and also including cancers of the gallbladder. And collectively, the key points are that these are poor prognosis cancers.

1001
03:07:09.180 --> 03:07:18.270
TELEPHONE_USER: and the majority of patients succumb to disease within about 12 months of diagnosis for the preponderance that have a locally advanced or advanced unresectable disease.

1002
03:07:18.350 --> 03:07:30.139
TELEPHONE_USER: and these are patients with high degree of morbidity, due to the complexity of their anatomy, frequently, including biliary tract infections and obstructions which can be treatment limiting particularly for conventional chemotherapies.

1003
03:07:30.350 --> 03:07:41.179
TELEPHONE_USER: Now, increasingly, we're seeing that a subset of patients do have targetable molecular alterations, including about 20%

that have her 2 amplification or overexpression

1004
03:07:41.550 --> 03:07:42.560
TELEPHONE_USER: next slide.

1005
03:07:48.660 --> 03:08:04.309
TELEPHONE_USER: This is a somewhat busy slide, but the point here is to show that our primary treatment option has now evolved to be the combination of gemcitabine plus cispat and chemotherapy, a long-held standard, with the addition of an immune checkpoint inhibitor, either Divumab or Pembrolizumab, based on phase, 3 data.

1006
03:08:04.450 --> 03:08:32.669
TELEPHONE_USER: the second row, the subsequent line therapy, however, is where we have a great unmet. Need. We have several standard chemotherapy options, including the preferred regimen per the Nccn guidelines of fulfox, based on the ABC. 0 6. Phase 3. Trial, but highlighted in the call-out box below. Unfortunately, these regimens leave much to be desired with very limited efficacy for the reference of Fox, for example, achieving a median overall survival of only 6.2 months.

1007
03:08:32.670 --> 03:08:49.430
TELEPHONE_USER: with progression-free survival of only 4 months and a rather dismal response rate of only 5%. And the outcomes for these other regimens of standard therapies which are based on only phase. 2 data are equally limited. So there's a very high unmet need in the second line and later line therapy setting.

1008
03:08:49.957 --> 03:08:51.360
TELEPHONE_USER: Next slide, please.

1009
03:08:54.270 --> 03:09:07.769
TELEPHONE_USER: Now, one thing that's been quite encouraging in biliary tract cancers is the emergence of molecularly targeted subgroups, molecularly targetable subgroups including patients with Fdfr. 2 fusions or idh one mutations, and I'll draw your attention to the bottom right

1010
03:09:07.770 --> 03:09:34.590
TELEPHONE_USER: for her. 2 positive tumors again, recalling those are up to around 20% of biliary tract cancers. There are several options based on small cohorts from basket trials, as shown here. Each of

these, though, does have some liabilities and is based on very limited data sets and can be limited by patients underlying liver function or ineligibility for chemotherapy. So this remains an area of unmet need, but we do see a signal of benefit from her 2 targeted therapy

1011
03:09:35.770 --> 03:09:36.829
TELEPHONE_USER: next slide.

1012
03:09:40.140 --> 03:10:06.349
TELEPHONE_USER: So Xanidatumab is a novel bispecific. Her 2 directed antibody with a recently labeled name of Zyhara, and it is a bispecific with multiple mechanisms of action specifically binding 2 extracellular sites on the her 2 receptor that can lead to effects due to internalization of the receptor leading to reduction of her 2 extracellular expression, also immune mediated antitumor efficacy through complement, dependent cytotoxicity.

1013
03:10:06.350 --> 03:10:10.370
TELEPHONE_USER: antibody drug cytotoxicity and phagocytosis.

1014
03:10:10.860 --> 03:10:16.240
TELEPHONE_USER: And it's not a T-cell engager, and it does not include standard chemotherapy next slide.

1015
03:10:20.580 --> 03:10:44.820
TELEPHONE_USER: So the trial that led to the approval of Zyhara in biliary tract cancers was horizon, Btc. 0, 1. This was a phase 2 B. Study of Xanidatumab in patients with previously treated her 2 amplified Btc. And in the dark blue box in the middle we can see that the study was divided into 2 cohorts. The 1st cohort were patients with immunohysiochemistry positive, 2 plus or 3 plus using gastric cancer scoring algorithms.

1016
03:10:44.820 --> 03:10:54.500
TELEPHONE_USER: while cohort 2 had patients with immunohistochemistry 0 or one plus patients were treated with Xanidatumab 20 milligrams per kilogram. Iv. Every 2 weeks

1017
03:10:54.990 --> 03:11:04.039
TELEPHONE_USER: up until progression, with primary endpoint of objective response rate and key secondary endpoints, including duration of response disease control, pfs, OS and safety.

1018
03:11:05.670 --> 03:11:18.589
TELEPHONE_USER: and the key point here also is for the bla, the cohort being examined are the 62 patients with Ihc. 3 plus by central assessment comprising the majority of patients in cohort one

1019
03:11:19.530 --> 03:11:20.530
TELEPHONE_USER: next slide.

1020
03:11:23.840 --> 03:11:32.630
TELEPHONE_USER: So here are the demographics from the horizon. Btco. One trial we can see that the Median age was about 64 years in cohort. One

1021
03:11:33.110 --> 03:11:42.079
TELEPHONE_USER: slightly more patients were female. There was a preponderance that were Asian, about 65% overall in cohort one. This reflects the demographics of biliary tract cancers

1022
03:11:42.310 --> 03:12:02.490
TELEPHONE_USER: and patients reflected a real world population, as you can see on the box on the right, with a variety of prior therapies. All patients had to have had at least one prior systemic gemcitabine based therapy, and about 33% had a second or more line of therapy. Again, reflecting our typical second line, patient population in the real world, second or later line next slide.

1023
03:12:06.360 --> 03:12:31.189
TELEPHONE_USER: So here are the primary endpoint efficacy data showing an objective response rate from for Xanabidatimab in cocort one Ihc. 3, plus her 2 patients comprising 62 patients. Objective response rate was 52%, including 3% with complete responses and 48% with partial responses. These responses were quite durable. The Median duration of response of 14.9 months

1024
03:12:31.550 --> 03:12:49.169
TELEPHONE_USER: and shown in the bottom. 3 rows are the comparator data. Again, just to remind us where we are in the second line setting with standard therapies for Fullfox, the response rate is only 5%. Thus, any data map here is achieving a response rate of about tenfold higher than standard chemotherapy options

1025
03:12:50.510 --> 03:12:51.550

TELEPHONE_USER: next slide.

1026
03:12:56.150 --> 03:13:16.109
TELEPHONE_USER: So the meaningful meaning excuse me. The overall survival also demonstrated a meaningful finding of 18.1 months for the Ihc. 3 plus Ela population within horizon, 0 point Btc 0 point 1. And again, this is substantially greater than what we'd expect from standard chemotherapy with the full fox comparator achieving a survival.

1027
03:13:16.110 --> 03:13:17.379
Catherine Bernstein: 3 min remaining.

1028
03:13:17.380 --> 03:13:18.220
TELEPHONE_USER: Context.

1029
03:13:18.960 --> 03:13:25.109
TELEPHONE_USER: the Median progression-free survival was 7.2 months again, much longer than what we expect in standard chemotherapy of 4 months.

1030
03:13:25.520 --> 03:13:26.590
TELEPHONE_USER: Next slide.

1031
03:13:29.140 --> 03:13:55.200
TELEPHONE_USER: Here are the safety data, the key safety data. The most common adverse event was diarrhea occurring in 50% of patients. The majority of these were grade of one or 2 with grade 3 only in 10% there were no grade. 4 or 5 infusion-related reactions was the next most common adverse event. At 35% majority. Again, grade one or 2, only 1% grade 3. All patients required premedication with Tylenol.

1032
03:13:55.280 --> 03:14:10.040
TELEPHONE_USER: second, hydramine and a steroid to reduce the risk of infusion-related complications resulting in this manageable profile. Only 2.5% of patients required discontinuation due to adverse reactions, and only 4% required dose reductions

1033
03:14:11.220 --> 03:14:12.300
TELEPHONE_USER: next slide.

1034

03:14:15.920 --> 03:14:44.720
TELEPHONE_USER: This slide shows quality of life and patient reported outcome findings that generally reinforce that the objective response rate and safety findings are meaningful on the patient's clinical experience, and on the left-hand panel we see quality of life scores in the blue bars, the dark blue bars showing an improvement in quality of life, various quality of life, parameters for patients who achieved a partial or greater response, again reinforcing that these responses are clinically meaningful to the patient experience.

1035
03:14:44.720 --> 03:14:54.960
TELEPHONE_USER: On the right we see a visual analog scale measurement showing that the patients with partial responses in the blue improved their vas scores again reinforcing clinically meaningful outcomes.

1036
03:14:55.040 --> 03:14:56.110
TELEPHONE_USER: Next slide.

1037
03:14:58.240 --> 03:15:17.269
TELEPHONE_USER: Likewise, we see a greater improvement in pain or reduction in worse pain for patients with complete or partial response caught out in the red box on the left hand panel, and on the right we see lower rates of opioid use for patients with response, again reinforcing that these durable objective responses are meaningful.

1038
03:15:17.270 --> 03:15:18.640
Catherine Bernstein: 1 min remaining.

1039
03:15:19.830 --> 03:15:20.770
TELEPHONE_USER: Next slide.

1040
03:15:23.270 --> 03:15:51.030
TELEPHONE_USER: So in summary biliary tract cancers are a rare and very morbid cancer, increasing in prevalence and incidence worldwide, most patients develop advanced unresectable disease and progress on first-line therapy requiring second line therapy. Our current second line therapies leave much to be desired with very minimal efficacy to date, though we do see a signal benefit from her 2 targeted therapies. Xanadatimab or Zyhera is a novel bispecific. Her 2 directed antibody

1041
03:15:51.030 --> 03:15:59.129
TELEPHONE_USER: with multiple mechanisms of response which has now shown the highest objective response rate in a Btc specific trial

targeting her 2

1042
03:15:59.330 --> 03:16:05.019
TELEPHONE_USER: and has a favorable safety profile and positive impact on patient quality of life.

1043
03:16:05.610 --> 03:16:08.799
TELEPHONE_USER: Thank you so much for your attention, and happy to take any questions.

1044
03:16:10.850 --> 03:16:14.599
Drew Kasper: Thank you for your presentation, and we'll start with questions from the public

1045
03:16:15.730 --> 03:16:19.370
Drew Kasper: as a reminder. The Q. And A. Is available for questions

1046
03:16:19.810 --> 03:16:30.939
Drew Kasper: and a raise hand will also allow us to know that you have a question, and we can enable you to unmute yourself and ask verbally if that's your preference.

1047
03:16:32.370 --> 03:16:40.909
Drew Kasper: I don't see any raise hands or questions in the Q. And a. And we don't have any new questions in the new tech mailbox.

1048
03:16:41.120 --> 03:16:47.280
Drew Kasper: which is the method for folks that are on the phone only and don't have the other options. So

1049
03:16:47.400 --> 03:16:58.619
Drew Kasper: we'll move on to open up questions from my colleagues at Cms. If anyone from the public has questions you can still ask now. But we're going to broaden it to open for questions from Cms.

1050
03:16:59.420 --> 03:17:02.420
Drew Kasper: You can go ahead and unmute. Now, if you have questions.

1051
03:17:04.020 --> 03:17:15.430
Andrew Wang: Hi, this is Andrew from Cms. I have a couple questions

for you. Given the at-risk population with advanced Btc. Would you comment on the demographic data of the patients included

1052
03:17:15.530 --> 03:17:16.790
Andrew Wang: in this data.

1053
03:17:19.450 --> 03:17:41.970
TELEPHONE_USER: Yes, so I'd say the age and gender demographic reflects the real world population we see in the Us. And the Asian predilection seen in the study reflects not only the study sites, but also the fact that certain risk factors for biliary tract cancers, including exposure to underlying liver diseases, whether hepatitis B, or C. Virus or prior fluke infection.

1054
03:17:41.970 --> 03:17:57.369
TELEPHONE_USER: are enriched in Asian populations, whether in Asia or in the Us. So our patient populations here in the clinic I'm in San Francisco. Do have a much higher proportion of patients which are Asian. My, my clinic is probably 40 plus percent Asian for biliary tract cancers here in the Us.

1055
03:17:57.930 --> 03:17:59.339
TELEPHONE_USER: Does that answer your question?

1056
03:18:00.360 --> 03:18:01.540
Andrew Wang: Yes, thank you so much.

1057
03:18:01.680 --> 03:18:11.059
Andrew Wang: And then my next question is, are the patients in the response group? Both ihc. 3 plus and ihc. 3, ihc. 2 plus.

1058
03:18:13.590 --> 03:18:26.040
TELEPHONE_USER: So the bla population is the IC 3 plus, which were 62 patients out of the 80 in cohort one. So the data I've shared on response rate of 52% is the IC 3 plus

1059
03:18:26.260 --> 03:18:36.849
TELEPHONE_USER: the overall response rate for the cohort. One was about 41%, indicating that the response rate for it 2 plus is substantially lower, and they are not included in the bla population.

1060

03:18:38.410 --> 03:18:39.170
Andrew Wang: Understood.

1061
03:18:39.350 --> 03:18:48.520
Andrew Wang: And then do you have any data isolating adverse events for her? 2 plus ih. 3 plus Btc. Which was the indication.

1062
03:18:50.280 --> 03:18:52.910
TELEPHONE_USER: You mean safety events, or.

1063
03:18:54.090 --> 03:18:54.660
Andrew Wang: Yes.

1064
03:18:54.660 --> 03:18:55.760
TELEPHONE_USER: Responsiveness.

1065
03:18:56.480 --> 03:18:57.700
TELEPHONE_USER: Let's see this safety.

1066
03:18:58.220 --> 03:19:02.109
TELEPHONE_USER: Were for the sorry. Could you rephrase, rephrase that.

1067
03:19:03.580 --> 03:19:13.039
Andrew Wang: Yeah, of course. Do you have any data isolating adverse events for the her 2 plus ih. 3 plus Btc, which was the FDA indication for this.

1068
03:19:14.520 --> 03:19:30.579
TELEPHONE_USER: Got it. I think that exists. I don't have it offhand, but my understanding was, there was no significant difference. For the 62 that were IC. 3 plus versus those that were 2 plus the one counterpoint would be that the patients who had 3 plus certainly had longer duration of exposure

1069
03:19:30.710 --> 03:19:35.809
TELEPHONE_USER: because they had dramatically higher response rates. And so one would expect temporally

1070
03:19:36.130 --> 03:19:43.900
TELEPHONE_USER: higher rates of events just by being on trial longer.

But otherwise I don't think there was any difference, and we'll we'll get back to you about that to confirm.

1071
03:19:44.910 --> 03:19:46.189
Andrew Wang: Very good. Thank you so much.

1072
03:19:51.020 --> 03:20:04.280
Adina Hersko: Hi, this is Adina at Dms. Just a question about the trial inclusion criteria. I believe it was for locally advanced and metastatic. And how does that compare to the FDA indication?

1073
03:20:06.380 --> 03:20:11.230
TELEPHONE_USER: That is really identical to the FDA indication.

1074
03:20:11.610 --> 03:20:19.369
TELEPHONE_USER: The I think we have unresectable. Locally advanced or metastatic, was the inclusion criteria for the trial and

1075
03:20:20.310 --> 03:20:22.960
TELEPHONE_USER: the label indication, I think, matches that.

1076
03:20:24.510 --> 03:20:25.120
Adina Hersko: The FDA.

1077
03:20:25.120 --> 03:20:33.210
TELEPHONE_USER: Previously treated under unresectable or metastatic, and so unresectable, and local events are synonymous in the clinical experience.

1078
03:20:33.470 --> 03:20:35.990
Adina Hersko: Thank you for clarifying. Also.

1079
03:20:35.990 --> 03:20:40.109
TELEPHONE_USER: A specific definition for locally advanced beyond unreceptible.

1080
03:20:41.060 --> 03:20:42.479
Adina Hersko: Thank you for clarifying.

1081

03:20:42.680 --> 03:20:52.279
Adina Hersko: Can you talk more about potential comparisons with and her 2, the other, her 2 directed targeted therapy you had discussed in the beginning.

1082
03:20:53.670 --> 03:21:15.209
TELEPHONE_USER: Sure. No, I think they both have really encouraging efficacy and reinforced the viability of the target clinically, I think there are key distinctions, including predominantly that in her 2 is an Adc. With a chemotherapy payload. And so, as I mentioned in the very beginning, a lot of our patients with advanced biliary tract. Cancers, after coming off of 1st line therapies.

1083
03:21:15.290 --> 03:21:42.819
TELEPHONE_USER: may not always be eligible for further chemotherapy, or may have some contraindications, including cycles of cholangitis or infection that preclude myelosuppressive therapies with anything that lowers blood counts, increasing their chances of getting a biliary tract infection. So there are a key subset of patients where a drug that does not cause myelosuppression or infection would be extremely favorable, and that we, for patients for whom we cannot use a cytotoxic in some cases due to infection, and our biliary tract, obstruction.

1084
03:21:43.330 --> 03:21:48.600
TELEPHONE_USER: sensitivity to biliary obstruction is also an issue for chemotherapies metabolized

1085
03:21:48.710 --> 03:21:58.780
TELEPHONE_USER: by the liver. And so patients who have borderline obstruction who are needing frequent stent changes would be much better served by a non hepatically metabolized agent.

1086
03:22:00.740 --> 03:22:01.490
Adina Hersko: Thank you.

1087
03:22:06.650 --> 03:22:09.939
Drew Kasper: Are there any other questions from Cms or the public?

1088
03:22:13.310 --> 03:22:18.430
Drew Kasper: There are no hands raised, and no new questions in the Q. And a.

1089
03:22:18.790 --> 03:22:20.739
Drew Kasper: Or in the intent mailbox.

1090
03:22:20.900 --> 03:22:25.859
Drew Kasper: Okay, so with that, thank you again for your presentation.

1091
03:22:26.160 --> 03:22:29.029
Drew Kasper: and we will now move into

1092
03:22:29.530 --> 03:22:32.980
Drew Kasper: our last break session of the day

1093
03:22:33.690 --> 03:22:41.449
Drew Kasper: and feel free to leave your computers on and just mute, and we'll see you

1094
03:22:41.670 --> 03:22:45.500
Drew Kasper: back here at 1, 1511 min

1095
03:22:50.130 --> 03:22:51.850
Drew Kasper: will be.

1096
03:22:52.880 --> 03:23:01.219
Drew Kasper: We'll be beginning here in just a minute as a reminder for the public, you can use the Q&A function or the raise hand function

1097
03:23:01.320 --> 03:23:18.399
Drew Kasper: to ask questions during the Q, and a portion after each presentation. Each presentation is 10 min long, with approximately 5 min for Q&A. The 10 min is a static time, the Q. And a. We try to let run. If if there are additional questions.

1098
03:23:20.220 --> 03:23:30.580
Drew Kasper: we will now begin with a presentation from tech hour

1099
03:23:31.040 --> 03:23:36.950
Drew Kasper: you can go ahead and unmute yourself and introduce

yourself. Please. Thanks.

1100
03:23:37.360 --> 03:23:48.739
Sandra P. D'Angelo: Yes. Hi, good afternoon. My name is Sandra d'angelo. I'm a medical oncologist at Memorial, Sloan Kettering Cancer Center, and I'll be presenting the data with regards to cellar

1101
03:23:49.790 --> 03:23:51.330
Sandra P. D'Angelo: next slide.

1102
03:23:53.950 --> 03:24:10.050
Sandra P. D'Angelo: So Teselra is actually the 1st and only FDA approved therapy for patients with metastatic and unresectable synovial sarcoma. This is a T-cell therapy that targets may J. 4.

1103
03:24:10.390 --> 03:24:23.870
Sandra P. D'Angelo: And it's for patients who specifically have metastatic and unresectable disease who have received prior chemotherapy, who have specific Hla O. 2 0, 1, or 202 0. 203, or 206,

1104
03:24:24.160 --> 03:24:34.200
Sandra P. D'Angelo: and whose tumor expresses Mayg. 4. As determined by the FDA-approved or cleared Companion Diagnostic Companion.

1105
03:24:34.210 --> 03:24:54.179
Sandra P. D'Angelo: This was orphan drug designated in August 2019, and then the regenerative medicine advanced therapy designated in November 2019 it was priority reviewed January 31, st 2024, and it was granted FDA accelerated approval on August 1, st 2024,

1106
03:24:54.610 --> 03:24:55.900
Sandra P. D'Angelo: next slide.

1107
03:25:01.190 --> 03:25:17.189
Sandra P. D'Angelo: So Teselvera is the 1st and only FDA approved engineered T cell receptor, T-cell therapy. It's the 1st and only FDA approved specifically for patients with metastatic or unresectable synovial sarcoma.

1108
03:25:17.310 --> 03:25:38.210
Sandra P. D'Angelo: This represents a new treatment. Options for these

patients who are unresponsive to existing systemic therapies after 1st line progression due to limited effectiveness, overall response rates and overall survival. This actually offers a significant clinical improvement in both response, rate and survival as compared to existing therapies.

1109
03:25:38.730 --> 03:25:44.349
Sandra P. D'Angelo: And it's well tolerated and has a manageable safety profile next slide.

1110
03:25:46.630 --> 03:25:58.580
Sandra P. D'Angelo: With regards to the mechanism of action. This is an engineered T cell receptor that targets an Antigen called Meiji 4.

1111
03:25:58.690 --> 03:26:11.640
Sandra P. D'Angelo: This is administered as a single one-time patient specific therapy. And, as I already mentioned, there's a specific requirement for the Hla alleles, which I already noted.

1112
03:26:12.070 --> 03:26:13.510
Sandra P. D'Angelo: Next slide

1113
03:26:15.580 --> 03:26:38.549
Sandra P. D'Angelo: a little bit about sarcoma and synovial sarcoma. Synovial sarcoma represents 5 to 10% of cases of soft tissue sarcomas. There's about 1,340 new cases diagnosed in the United States each year. The Median age of presentation is 39, about 11% of patients with synovial sarcoma are older than 65,

1114
03:26:38.630 --> 03:26:47.510
Sandra P. D'Angelo: 15% of patients present with metastatic disease at the time of diagnosis and the median duration of symptoms before diagnosis can be up to 2 years.

1115
03:26:47.810 --> 03:26:55.130
Sandra P. D'Angelo: There's a diversity of symptoms and tumor locations that define this particular disease.

1116
03:26:55.260 --> 03:27:01.599
Sandra P. D'Angelo: and patients tend to be younger, and that can often lead to a misdiagnosis.

1117
03:27:02.430 --> 03:27:03.610
Sandra P. D’Angelo: Next slide

1118
03:27:05.950 --> 03:27:18.009
Sandra P. D’Angelo: a little bit about prognosis. The one year survival for the disease is quite poor. It's only 60%. The 5 year survival is approximately 20%. The 10 year survival is less than 15%.

1119
03:27:18.120 --> 03:27:28.200
Sandra P. D’Angelo: The median overall survival for patients with metastatic synovial sarcoma on second line therapy is just 11.7 months. So this is a dismal disease next slide.

1120
03:27:32.830 --> 03:27:55.920
Sandra P. D’Angelo: So Tecilera offers a new option for patients with this diagnosis. Just to put this into context, these are some of the existing therapy options that we have to offer. Pizopinib is an oral pill, a tyrosine kinase inhibitor that offers a response rate of about 19%. The Median survival is 10.3 months.

1121
03:27:55.920 --> 03:28:10.410
Sandra P. D’Angelo: Tribectin offers an option as well. If the response rate is 12% and the median survival is 10.4 months. I'll highlight that Trabectin is actually not FDA approved, though, in the United States for synovial sarcoma.

1122
03:28:10.600 --> 03:28:19.070
Sandra P. D’Angelo: gemcitabine and docetaxel is an alternative a cytotoxic chemotherapy regimen that we often use in high grade sarcomas.

1123
03:28:19.460 --> 03:28:33.569
Sandra P. D’Angelo: And in this specific sarcoma the response rate's about 5% survival is 8 to 14 months, and then Rigorafenib is an oral tyrosine kinase, inhibitor similar to pizopinib with a response rate of 8%.

1124
03:28:33.670 --> 03:28:42.859
Sandra P. D’Angelo: And the Median survival 13.4 months. I'll also highlight, though, that ragorafenib is not FDA approved either for synovial sarcoma

1125
03:28:42.990 --> 03:28:44.290
Sandra P. D’Angelo: next slide.

1126
03:28:46.660 --> 03:29:05.120
Sandra P. D’Angelo: These are the eligibility criteria in the study schema in order to participate in the spearhead. One clinical trial which was used for analysis for FDA approval. Patients must have had inoperable or metastatic synovial sarcoma.

1127
03:29:05.120 --> 03:29:20.079
Sandra P. D’Angelo: the specific Hla alleles, as noted on the slide expression of Mayj 4. They must have received prior system. Therapy have measurable disease, persist 1.1 appropriate performance status of 0 1

1128
03:29:20.260 --> 03:29:44.690
Sandra P. D’Angelo: and adequate kidney function with a Gfr. Greater than or equal to 60 milliliters per minute. The study initiated with screening for the specific eligibility requirements for Hla, followed by Mayj. 4, once deemed eligible. Patients, then went on to leukophoresis and manufacturing of the product

1129
03:29:44.860 --> 03:30:05.110
Sandra P. D’Angelo: that was followed by lethal depletion, chemotherapy, infusion of t-selbra and then follow up for efficacy, safety, monitoring and translational studies cohort one and enrolled a total of 44 patients. The primary endpoint of the study was response rate, and there was a number of secondary endpoints as well.

1130
03:30:05.700 --> 03:30:06.950
Sandra P. D’Angelo: Next slide.

1131
03:30:11.350 --> 03:30:32.760
Sandra P. D’Angelo: These are the efficacy data that initially, we reported in Lancet in April 2024. So I'll highlight those responses. There was a partial response rate of 38.6%. The Median duration of response was 11.6 months

1132
03:30:33.080 --> 03:30:56.450
Sandra P. D’Angelo: for analysis for FDA approval. There was an additional central radiographic read of all the enrolled patients which led to some changes with regards to the efficacy endpoints with

that analysis. The response rate was 43%. There were 2 complete responses noted at that time, and.

1133
03:30:56.450 --> 03:30:56.960
Catherine Bernstein: Remaining.

1134
03:30:56.960 --> 03:30:59.640
Sandra P. D'Angelo: Once next slide

1135
03:31:02.340 --> 03:31:28.309
Sandra P. D'Angelo: there were a number of different clinical factors that were analyzed to be predictive of potential efficacy. Responses were noted amongst all of the cohorts. I'll highlight that. Responses were also seen in patients younger and older than 40 years. As would otherwise be expected, these results are generalizable to medicare populations.

1136
03:31:28.310 --> 03:31:36.370
Sandra P. D'Angelo: The Medicare population comprised approximately 7% of the study population. Those were patients that were older than 65,

1137
03:31:36.480 --> 03:31:41.989
Sandra P. D'Angelo: and all those patients had a valuable disease, and also were noted to have responses as well.

1138
03:31:42.230 --> 03:31:43.480
Sandra P. D'Angelo: Next slide.

1139
03:31:46.280 --> 03:31:54.899
Sandra P. D'Angelo: Here we have a slide which highlights the response rates for those patients that had responses.

1140
03:31:55.455 --> 03:32:07.510
Sandra P. D'Angelo: The Median overall survival was 16.9 months. Specifically, in those that responded that Median was not reached, that for those that did not respond. It was 10.9 months.

1141
03:32:09.350 --> 03:32:26.260
Sandra P. D'Angelo: The estimated probability in the 17 patients who actually had a resist response was 90% at 12 months and 70% at 24 months. And when we put this into context compared to pisopinib,

obviously, this is significantly better.

1142
03:32:27.029 --> 03:32:28.149
Sandra P. D'Angelo: Next slide.

1143
03:32:30.380 --> 03:32:34.340
Sandra P. D'Angelo: Here we have that comparison which I alluded to

1144
03:32:35.110 --> 03:33:01.659
Sandra P. D'Angelo: to Sellra's response rate is 38 ranges from 30 to 40 43.2%, and the median overall survival is 16.9 months, and you can see this is better than all the other prior standard regimens that we utilize in this disease, which offer response rates generally less than in most cases less than 10%, and the survival ranges from 10 to 13 months. Next slide.

1145
03:33:03.750 --> 03:33:13.369
Sandra P. D'Angelo: Safety obviously is important. The contents of these therapies. These are different than traditional therapeutics. What we commonly see

1146
03:33:13.390 --> 03:33:39.339
Sandra P. D'Angelo: is a cytokine release syndrome. Importantly, these were only grade 3 in 2% of patients. In addition, we saw that a Cytokine release syndrome was manageable. There was one case of icans which was grade one, and the important thing to highlight is obviously, as is the case with most cell therapies. This is a 1-time administration

1147
03:33:41.010 --> 03:33:42.260
Sandra P. D'Angelo: next slide.

1148
03:33:43.970 --> 03:34:03.309
Sandra P. D'Angelo: And so to summarize Tecelra is a major. 4 directed, genetically modified T cell receptor that's indicated for patients that have unresectable metastatic Stenobosarcoma who have received chemotherapy, who have the specific hla-o, 2 subtype positive

1149
03:34:03.440 --> 03:34:06.069
Sandra P. D'Angelo: and who expressed an ag. 4 antigen.

1150

03:34:06.711 --> 03:34:12.170
Sandra P. D’Angelo: We note that this meets the ntap sci criteria, that as it is a new.

1151
03:34:12.170 --> 03:34:13.350
Catherine Bernstein: It's been 10 min.

1152
03:34:13.720 --> 03:34:16.389
Sandra P. D’Angelo: And improves upon clinical outcomes. Early.

1153
03:34:16.390 --> 03:34:17.340
Drew Kasper: Yeah, we

1154
03:34:17.580 --> 03:34:35.819
Drew Kasper: I do need to stop you there. Sorry we're over time. We we have to keep it to 10 min to just be equitable across all the applicants. So sorry to interrupt you at the end there, but we can move on into into questions. Starting with questions from the public.

1155
03:34:39.910 --> 03:34:46.919
Drew Kasper: Do we have any questions from the public? I don't see anything in the Q&A. Or raised hands.

1156
03:34:48.450 --> 03:34:50.414
Drew Kasper: or in the

1157
03:34:52.040 --> 03:35:08.999
Drew Kasper: new tech mailbox. There are no new questions. So that means we'll open up questions to my colleagues at Cms. If those of you in the public still have questions, feel free to enter them in the Q. And a. Or raise a hand. But we'll move on to Cms. Questions.

1158
03:35:09.270 --> 03:35:12.409
Drew Kasper: Folks can now go ahead and unmute, and ask your questions.

1159
03:35:13.840 --> 03:35:18.759
Dorota Marchel: Hi, Dr. D'angelo, thank you for that presentation. This is Dorota Marshall with Cms.

1160

03:35:19.090 --> 03:35:37.950
Dorota Marchel: So I was wondering in the list of comparators that you know, were chosen to compare to Celra. I was wondering if you could clarify why, Ifopsamide or Ifopsamide based regimens were not included as an existing treatment option for these patients.

1161
03:35:38.310 --> 03:35:47.890
Sandra P. D'Angelo: That's a great question, though generally amtracycline based therapies with or without a opshamide are generally used in the frontline setting.

1162
03:35:48.080 --> 03:36:03.850
Sandra P. D'Angelo: and this study cohort actually occurred in the second line setting, you had to have received prior anthracycline and niphosponide based therapy. So for that reason it wasn't included as a comparator.

1163
03:36:05.000 --> 03:36:08.330
Dorota Marchel: So these were patients who potentially had failed. Ifopsamide.

1164
03:36:08.330 --> 03:36:09.400
Sandra P. D'Angelo: That's correct.

1165
03:36:09.400 --> 03:36:12.967
Dorota Marchel: Okay, and then

1166
03:36:13.830 --> 03:36:27.919
Dorota Marchel: the spearhead trial included only patients with specific biomarkers. Can you explain how these patients, compared to the broader, patient population with advanced synovial sarcoma that were tested in the trials for the existing therapies.

1167
03:36:28.889 --> 03:36:35.370
Sandra P. D'Angelo: Sure. So the biomarkers that are used to select patients

1168
03:36:36.350 --> 03:36:58.300
Sandra P. D'Angelo: do not vary and do not affect outcomes in the general Synovia sarcoma population. So, for example, Hla, we actually published and reported that for those patients with Synovia sarcoma harboring the specific Hla for which we selected patients for the

spearhead trial doesn't impact

1169
03:36:58.560 --> 03:37:08.529
Sandra P. D'Angelo: responses and duration of response to. For example, Pisopin based therapy. This was something that we published on Nccr. Probably in 2018

1170
03:37:09.265 --> 03:37:17.670
Sandra P. D'Angelo: and similarly a number of different Antigens, like Meiji, 4, such as Nyeso and Prime and

1171
03:37:17.910 --> 03:37:26.919
Sandra P. D'Angelo: and Major 4 as well. They've all been evaluated in the context of these diseases and have not really impacted outcomes.

1172
03:37:27.070 --> 03:37:48.290
Sandra P. D'Angelo: And so these antigens are required to select patients. Because that's how the therapy is used. You need to have the Hla. You need to have them. Aj, 4. But those particular biomarkers don't impact general outcomes to standard therapies as far as we've studied.

1173
03:37:49.430 --> 03:37:50.494
Dorota Marchel: Okay, thank you.

1174
03:37:51.618 --> 03:38:00.829
Dorota Marchel: And do you have any data on how the adverse events with Tecelra, compared to the adverse events of other existing technologies.

1175
03:38:01.920 --> 03:38:07.579
Sandra P. D'Angelo: So there is no actually comparator existing technology specifically.

1176
03:38:07.720 --> 03:38:25.110
Sandra P. D'Angelo: that exists. Ticelra is actually the 1st t cell therapy that's approved broadly, we can consider making comparisons to chimeric antigen receptors, which are car-ts which are currently approved in the hematological space.

1177
03:38:25.110 --> 03:38:38.219

Sandra P. D’Angelo: But, you know, it's not generally a fair comparison. The patient population, and the heat is more. Those patients with hematological malignancies to cellras approved for solid tumor patients.

1178
03:38:38.220 --> 03:38:51.140
Sandra P. D’Angelo: Because these therapies are generally similar. We can make some sort of broad generalizations in that, for example, Cytokine, release syndrome is something that we see.

1179
03:38:51.522 --> 03:38:57.329
Sandra P. D’Angelo: And and with Teselva it occurred grade 3 or higher, and only 2% of patients

1180
03:38:57.460 --> 03:39:21.640
Sandra P. D’Angelo: lowering of the blood counts or cytopenias is something else that we can see, and that's due to the lymphodepletion chemotherapy that we use. One distinction is that we didn't really see. A high incidence of eye cans again occurred in one patient, and it was grade. One and icans can occur in some of the hematological directed therapies.

1181
03:39:21.640 --> 03:39:28.993
Sandra P. D’Angelo: So yeah, I mean, overall the it's similar. But there's some nuances. And this is a technically a different

1182
03:39:29.620 --> 03:39:34.539
Sandra P. D’Angelo: therapy compared to the existing adoptive cell therapies that are approved at right now.

1183
03:39:35.660 --> 03:39:36.840
Dorota Marchel: Okay. Thank you.

1184
03:39:40.600 --> 03:39:58.040
Adina Hersko: Hi. This is Adina from Cms. Just as a follow up to that, I think we're looking for comparison of adverse events for Teselro, compared to other therapies for synovial sarcoma that are used. Other current therapies that you had listed on the slide. How would you compare the adverse events for both of those.

1185
03:39:58.370 --> 03:40:16.710
Sandra P. D’Angelo: So the distinction between Teselvera and other

existing therapies is that Teselvera is a 1-time infusion. You receive Lymphodepletion chemotherapy, and then you receive teselva. And then you're monitored during that period, and then you don't need any additional therapy.

1186
03:40:16.710 --> 03:40:32.129
Sandra P. D'Angelo: The current standard therapies that are used in the context of synovia, sarcoma are cytotoxic chemotherapeutics. So, for example, gemcitabine and docetaxel pisopinib, which require ongoing

1187
03:40:32.220 --> 03:41:01.409
Sandra P. D'Angelo: administration. And so in the context of those therapies the side effects are ongoing and persistent. And so, for example, you receive chemotherapy. A week later you have a decrease in your blood counts. You have nausea, you can have peripheral neuropathy. You can have cytopenias, you can have neutropenic fever, all of that resolves, and then you do it again 3 weeks later. So it's persistent and ongoing, which is a big distinction. Where

1188
03:41:01.410 --> 03:41:11.649
Sandra P. D'Angelo: with Teselva, you have these potential adverse events one time, and once you recuperate from that, essentially, you're done treating the disease.

1189
03:41:12.460 --> 03:41:32.679
Adina Hersko: Thank you. I also had just one clarifying question. If you could go back a couple of slides to where you had all the outcomes for the other therapies. This one right here and it says here for overall survival 16 months on the previous slide. It looked like the overall survival was 10 months. Can you? Can you clarify.

1190
03:41:34.473 --> 03:41:40.520
Sandra P. D'Angelo: No. So the overall survival across the cohort is 16.9 months. If

1191
03:41:40.710 --> 03:41:44.489
Sandra P. D'Angelo: yeah, that's the median right? That's the if you go back.

1192
03:41:46.950 --> 03:42:00.779
Sandra P. D'Angelo: That's the line in block. We divided this by responding and non-responding right? So if you are able to generate a

response to this therapy, the median hasn't yet been reached.

1193
03:42:00.950 --> 03:42:04.469
Sandra P. D’Angelo: But if you don't have a response, it's 10.9 months.

1194
03:42:04.470 --> 03:42:05.300
Adina Hersko: Got it. Okay, thanks.

1195
03:42:05.300 --> 03:42:10.840
Sandra P. D’Angelo: But the overall survival, when you look at the whole cohort is 16.9 months.

1196
03:42:11.320 --> 03:42:12.150
Adina Hersko: Thank you.

1197
03:42:18.510 --> 03:42:21.660
Drew Kasper: Are there any other questions from Cms or from the public.

1198
03:42:25.630 --> 03:42:26.590
Huub Kreuwel: What's happening.

1199
03:42:27.580 --> 03:42:35.429
Drew Kasper: If there are questions from other presenters, you can also, as a as a public attendee, ask questions.

1200
03:42:37.830 --> 03:42:40.320
Drew Kasper: Okay, there are no new questions in the Q. And a.

1201
03:42:41.260 --> 03:42:43.020
Drew Kasper: There are no raised hands.

1202
03:42:44.660 --> 03:43:01.140
Drew Kasper: and there are no new questions in the Cms new tech mailbox. Okay? All right. Well again. Thank you for your presentation. Sorry we had to cut you a little short there, and we will now move on to

1203

03:43:01.670 --> 03:43:07.680
Drew Kasper: the presentation for fibria. You may now unmute and introduce yourself.

1204
03:43:07.680 --> 03:43:27.360
Huub Kreuwel: Sure. Hi, so my name is Adam Gerber. I'm an anesthesiologist by training, and I'm the medical director for critical care at Octapharma. And so we're here to discuss our product fibrigo, which is the 1st and only fibrinogen concentrate, approved for acquired fibrinogen deficiency in bleeding patients. So we can go to the next slide, please.

1205
03:43:28.640 --> 03:43:42.200
Huub Kreuwel: So most people don't think about it. But bleeding is a major cause of death in the United States. Looking at really the 3 major groups where we see a lot of it, trauma is about 2.6 million hospital admissions.

1206
03:43:42.220 --> 03:44:00.569
Huub Kreuwel: 40% of these deaths are due to hemorrhage. And what's really important to remember is, we think of trauma as a young person's disease. But as we age now about over the age of 65, about 40% of all trauma admissions are now over the age of 65. In the United States

1207
03:44:00.660 --> 03:44:24.390
Huub Kreuwel: we also see a lot of bleeding in postpartum hemorrhage patients, which accounts for about 12% of maternal deaths, and in cardiac surgery as well, which skews towards patients that are generally older than 65 with 5 to 10% of them experiencing major bleeds and developing coagulopathies due to contact activation with the cardiopulinary bypass circuit

1208
03:44:24.540 --> 03:44:25.559
Huub Kreuwel: next slide.

1209
03:44:27.200 --> 03:44:51.380
Huub Kreuwel: So what's important to remember, is fibrinogen is very important. It's the last step of the coagulation cascade, and it's the molecule that forms fibrin which forms a net which seals off the clot and stops bleeding. So you really need it to maintain hemostasis and low levels have correlated with poorer outcomes in trauma levels under 1.5 show increases in 28 day mortality

1210
03:44:51.380 --> 03:45:12.119
Huub Kreuwel: in obstetrics levels below 2 means you will almost certainly progress to a severe postpartum. Hemorrhage, and in cardiac surgery varying levels have shown association with increased transfusion requirements, increased post-operative bleeding and longer icu state, so increasing the burden on patients in the healthcare system.

1211
03:45:12.140 --> 03:45:13.190
Huub Kreuwel: Next slide.

1212
03:45:14.520 --> 03:45:38.289
Huub Kreuwel: So what is fibrigo? So it is a human fibrinogen concentrate that we extract from large multi-donor pools of plasma via fractionation. It's pathogen inactivated which enhances safety and it really addresses an unmet need for a readily available shelf stable, precise and safe source of fibrinogen to treat acquired fibrinogen deficiency in bleeding patients

1213
03:45:38.450 --> 03:45:49.399
Huub Kreuwel: it's the 1st fibrinogen concentrate that's been approved for this use, and it is a dried, lyophilized powder that can be reconstituted very quickly. Next slide

1214
03:45:51.210 --> 03:46:04.090
Huub Kreuwel: so just briefly, the manufacturing process. The pathogen removal is done via a solvent detergent and activation. It's after that happens which kills lipid, enveloped viruses. Nanofiltration is then performed

1215
03:46:04.090 --> 03:46:22.810
Huub Kreuwel: which removes the non-enveloped viruses. And then there's Ion exchange chromatography done that purifies the product, removes anything that's not supposed to be in there, and very importantly removes residual coagulation factors. So you know, you're really delivering a pure fibrinogen to these patients

1216
03:46:23.160 --> 03:46:24.149
Huub Kreuwel: next slide.

1217
03:46:26.200 --> 03:46:48.450
Huub Kreuwel: So because of this process and the way it's produced, it

offers several clinical advantages over the standard of care which is cryoprecipitate, which is the blood component that's used typically used right now to replace fibrinogen in bleeding. Patients so cryoprecipitate is not pathogen inactivated. So, despite screening, there's still a risk of a blood-borne infection. Transmission.

1218
03:46:48.480 --> 03:46:59.300
Huub Kreuwel: cryoprecipitate also has very variable levels of fibrinogen versus fibrigo which is very standardized about one gram per vial. So providers always know what they're giving.

1219
03:46:59.440 --> 03:47:07.880
Huub Kreuwel: Fibrica has a lower infusion volume which becomes a concern when you're resuscitating patients. As higher volumes are associated with poorer outcomes.

1220
03:47:08.130 --> 03:47:28.729
Huub Kreuwel: Cryoprecipitate, requires thawing. It delays administration by about 30 to 45 min, whereas fibrica can be reconstituted in about 5 to 10 min, and this is extraordinarily important, because we know that for every minute you delay the delivery of blood products to a bleeding, patient mortality can increase by around 5%.

1221
03:47:28.730 --> 03:47:42.189
Huub Kreuwel: There's no abo testing required. We're universal. We have a long shelf life about 4 years in room temperature, storage versus cryo, which is a year frozen. So there's a very high possibility of wastage.

1222
03:47:42.360 --> 03:48:05.530
Huub Kreuwel: There's in cryo. There seems to be a higher risk of thrombosis due to the factor 8. And von Wildebrand's factor that probably come along for the ride in cryoprecipitate, whereas we have none of that, and we have, because of the way the product is cleaned, we have a lower risk of transfusion reactions such as allergic reactions when a blood product is given to a patient next slide.

1223
03:48:07.520 --> 03:48:37.269
Huub Kreuwel: So because of its properties, we can have a rapid delivery in emergency situations. So we're stable at room temperature for 48 months, which means unlike cryoprecipitate which has to sit in the Blood Bank. We can be stored near point of care locations, so we can be in trauma carts, maternal hemorrhage carts, anesthesia,

workstations, nursing omni cells and area pharmacies close to where the patient that needs to be treated is, which is a very big deal in these acute situations.

1224
03:48:37.270 --> 03:49:00.490
Huub Kreuwel: so clinicians would have very rapid access to fibrinogen during critical emergencies which they don't currently have. The cryo is very difficult to get, and reconstitution only takes 5 to 10 min versus again, the long delivery time for cryoprecipitate. And if you look at studies that have compared the delivery of cryoprecipitate versus fibrinogen concentrate in trauma patients.

1225
03:49:00.660 --> 03:49:14.329
Huub Kreuwel: It's about half the time to deliver a round of fibrinogen. Concentrate versus cryoprecipitate, and we know that faster delivery seems to improve survival rates in major bleeding events next slide.

1226
03:49:17.040 --> 03:49:21.091
Huub Kreuwel: Okay, next slide, please. There we go. Oh, wait back one

1227
03:49:22.370 --> 03:49:23.870
Huub Kreuwel: think we went one too far

1228
03:49:25.080 --> 03:49:28.783
Huub Kreuwel: there. We no one or no, maybe we didn't. Sorry. Go ahead, go forward again.

1229
03:49:29.280 --> 03:49:52.899
Huub Kreuwel: So you know, one of the other things that Fibrica can do is reduce the usage of blood products. So one of the benefits. If you look at a meta-analysis that look at the use of fibrinogen concentrates across several surgeries, they reduce the transfusion of allogeneic blood products. This reduction in transfusion is associated with improved, patient outcomes

1230
03:49:52.940 --> 03:49:59.640
Huub Kreuwel: because, you know, blood products. It is like performing a transplant on a patient, and all those associated risks.

1231
03:49:59.800 --> 03:50:19.230
Huub Kreuwel: If you look specifically at the retrospectively, at the

use of fibrinogen concentrates and trauma, you can also see a significant reduction in blood component usage within the 1st 24 h. Shorter hospital stays shorter icu length of stay. And generally, when you reduce these things and you reduce the use of blood products. Studies have.

1232
03:50:19.230 --> 03:50:20.290
Catherine Bernstein: 3 min remaining.

1233
03:50:20.290 --> 03:50:29.589
Huub Kreuwel: Save a significant amount of money as well as increased improved outcomes for patients next slide.

1234
03:50:34.090 --> 03:50:55.940
Huub Kreuwel: So on top of the reducing the usage of blood products. The fast delivery pathogen inactivation provides another margin of safety. So, despite the fact that the blood supply is rigorously screened, there is still a risk of transmitting infectious agents through the blood, through blood transfusions. And the FDA. In fact, advocates for the use of these types of products whenever possible.

1235
03:50:55.940 --> 03:51:19.329
Huub Kreuwel: We know what we test for. We don't know what's coming out there right now. So this is a very important safety measure for patients to have and so solvent detergent treatment. Nanofiltration allows us to achieve about a 99.9 9% reduction in viral titers which provides a significantly higher margin of safety compared to the screening alone that's performed on blood components like cryoprecipitate

1236
03:51:19.440 --> 03:51:20.520
Huub Kreuwel: next slide.

1237
03:51:22.720 --> 03:51:45.240
Huub Kreuwel: So Fibrica has been involved in 5 separate studies that's demonstrated its safety and efficacy in adult and pediatric populations for both the congenital forms of fibrinogen deficiency and the acquired form due to bleeding. It received approval based on the fibr study, which was done in cardiac surgery, which looked at 735 patients, and showed that

1238
03:51:45.430 --> 03:52:04.019
Huub Kreuwel: that in terms of allogeneic blood products transfused

within the 1st 24 h. Fibrica was clinically non-inferior to cryoprecipitate. There was also a trend towards a lower number of Thromboembolic events in the Fibrica group which is consistent with the fact that you're probably not delivering

1239
03:52:04.140 --> 03:52:06.850
Huub Kreuwel: unneeded coagulation factors.

1240
03:52:06.990 --> 03:52:27.449
Huub Kreuwel: Fibrica was also looked at specifically in the forma. O 5 study which looked at major abdominal surgery. There we were able to show 46 min faster delivery to the or and consistent with the fibrous trial. Thromboembolic events. There were no thromboembolic events in the Fibrica group, and 7 events in the cryoprecipitate group next slide.

1241
03:52:29.060 --> 03:52:53.920
Huub Kreuwel: So in summary, so Fibrica is currently the only fibrinogen concentrate that's approved for the FDA for acquired fibrinogen deficiency. We can provide rapid access to a fibrinogen source in emergency situations that's currently not available to physicians treating Major Bleeds we're shelf stable with a 4 year shelf life which can reduce wastage, and let us be stored very easily near the point of care.

1242
03:52:53.920 --> 03:53:12.820
Huub Kreuwel: We have a high level of purity and safety, with known amounts of fibrinogen and pathogen inactivation to help protect patients. And so we think these criteria, compared to the standard of care, fulfill a newness criteria, and provide a substantial clinical improvement in the treatment of major bleeds. And I'll take any questions.

1243
03:53:15.230 --> 03:53:19.129
Drew Kasper: Thank you for your presentation, and we'll start with questions from the public.

1244
03:53:21.360 --> 03:53:28.150
Drew Kasper: We don't have any new questions in the chat, and

1245
03:53:29.730 --> 03:53:32.760
Drew Kasper: we don't have any raised hands.

1246
03:53:33.950 --> 03:53:39.400
Drew Kasper: There are no new questions in the new tech mailbox.

1247
03:53:39.710 --> 03:53:45.920
Drew Kasper: And so with that, we'll broaden the question pool

1248
03:53:46.020 --> 03:53:48.720
Drew Kasper: to that of my colleagues at Cms.

1249
03:53:49.600 --> 03:53:59.230
Drew Kasper: Those of you at Cms can go ahead and unmute now and chime in with your questions, and the public can continue to enter questions if and as you have them, thanks.

1250
03:54:00.750 --> 03:54:20.199
Andrew Wang: Thank you very much for the presentation. I did have a couple more questions for you. So did any of these studies that you showed, I believe it was slide 198. Compare Fibriga against any other brands of fibrinogen product, such as the intercepts pathogen reduced fibrinogen product.

1251
03:54:20.800 --> 03:54:50.770
Huub Kreuwel: So we've not had a comparison yet between the products. I actually think that's something that's going to be long overdue. But the thing to remember about the intercept product that is a pathogen, inactivated, cryoprecipitate. So it's really not comparable to fibrica. So Fibrica is regulated as it's a blood derivative. So we go through. We have batch testing. We know exactly what's in each vial, whereas the intercept comp and we're produced in a large manufacturing facility.

1252
03:54:50.770 --> 03:55:05.049
Huub Kreuwel: The intercept product is cryoprecipitate that's produced at a blood center undergoes an activation there and then is released under the same stringencies as a blood component. So it's not tested. So you only know

1253
03:55:05.050 --> 03:55:25.199
Huub Kreuwel: that there's more than 150 milligrams of fibrinogen per unit on top of all the other stuff that comes with it. So I think you know, and you still have the same issues with the intercept product in terms of delivery times. Right? It's kept in the Blood Bank, and even

though it can be stored, thawed, it still has to be delivered. You have higher volumes of infusion, so

1254
03:55:25.200 --> 03:55:42.729
Huub Kreuwel: I don't think they're comparable products. But I think a comparison of comparing fibrinogen concentrates to cryoprecipitate products is something that is overdue. But there's nothing out there right now to answer your question that compares them directly.

1255
03:55:44.480 --> 03:55:55.550
Andrew Wang: Thank you very much. And my next question is, were there any other improvements in clinical outcome measures attributable to Fibrica as a consequence of improved time to administration.

1256
03:55:56.140 --> 03:56:15.090
Huub Kreuwel: So nothing. We have nothing definitive that can show that that is, you know, this is the problem with bleeding trials in general is they're extraordinarily difficult to do. It is, you know, again, something we think about what we do know. Across

1257
03:56:15.320 --> 03:56:43.400
Huub Kreuwel: almost every study you look at in major bleeding. Is that the faster you administer you have a patient who's bleeding out, the faster you administer, the better they tend to do. And what's really important to remember about Fibrinogen? Why, there's certainly an argument that patients will likely do better. Fibrinogen is the 1st factor that falls in a bleeding patient. Within about an hour you reach a nadir, and if you don't have fibrinogen there, you're not going to clot.

1258
03:56:43.400 --> 03:56:46.260
Huub Kreuwel: and so that you have something that within

1259
03:56:46.260 --> 03:57:03.120
Huub Kreuwel: 10 min you can get this stuff into a bleeding patient may actually be able to prevent you from proceeding further down that cascade of bleeding events versus having to wait for stuff to come up from Blood Bank as someone who's been in that situation. I'll tell you. It's extraordinarily anxiety provoking.

1260
03:57:05.220 --> 03:57:07.590
Andrew Wang: Gotcha. Thanks so much for your answers.

1261
03:57:07.700 --> 03:57:08.660
Andrew Wang: Nothing else.

1262
03:57:17.270 --> 03:57:21.199
Drew Kasper: Do we have any additional questions from Cms or from the public?

1263
03:57:27.410 --> 03:57:29.700
Drew Kasper: There are no questions in the Q. And A.

1264
03:57:30.580 --> 03:57:37.640
Drew Kasper: There are no raised hands, and there are no new questions in the Newtek mailbox.

1265
03:57:40.000 --> 03:57:49.000
Drew Kasper: Okay, great. Well, thank you again for your presentation, and we will now

1266
03:57:50.470 --> 03:57:59.390
Drew Kasper: transition to the presenters from Ben Trasimab may now unmute and introduce yourself.

1267
03:58:03.180 --> 03:58:04.769
W. Frank Peacock: Hey? I'm Frank Peacock.

1268
03:58:05.850 --> 03:58:08.490
W. Frank Peacock: I'm going to be talking about ventresumab today.

1269
03:58:09.350 --> 03:58:10.690
W. Frank Peacock: Next slide, please.

1270
03:58:12.470 --> 03:58:19.000
W. Frank Peacock: These are my disclosures. I've been doing emergency medicine research for about 30 years. So I've acquired a few next slide.

1271
03:58:20.370 --> 03:58:25.480
W. Frank Peacock: So Ventrazumab is an investigable investigational treatment for the reversal of

1272
03:58:25.590 --> 03:58:28.580
W. Frank Peacock: the Antiplatelet, p. 2, y. 12. Ticagrelor.

1273
03:58:28.890 --> 03:58:38.770
W. Frank Peacock: It's novel investigational, monoclonal, antibody fragment, and it's being developed as a specific reversal agent for people on Ticagrelor.

1274
03:58:38.860 --> 03:58:59.919
W. Frank Peacock: When the effects of ticagrelor is needed and there are 2 cohorts in this trial that I'll show you. The one is the patients requiring non-deferable surgery. Ticagrelor, if you stop, it will hang on for about 5 days, at which point you can now do any surgery you want, but there are plenty of opportunities where you can imagine patients requiring surgery

1275
03:59:00.050 --> 03:59:11.399
W. Frank Peacock: who don't have 5 days to wait, and reversing the antiplatelet would be a good thing for those, and the other cohort is those who are experiencing major bleeding, and you need to reverse it to save their life.

1276
03:59:11.560 --> 03:59:31.560
W. Frank Peacock: Fj. Pharmaceuticals is the bla sponsor. The FDA submission sponsor Ben transmed, received breakthrough designation therapy in April 2019, and Priority Review in July of 2024. Their approval, date, or disapproval date, however, that works out at the FDA is 1st quarter of 2025

1277
03:59:31.700 --> 03:59:39.409
W. Frank Peacock: cerb pharmaceuticals bought the rights for this from Fj. And will be the company commercializing the tresumab next slide.

1278
03:59:42.430 --> 03:59:53.019
W. Frank Peacock: So when you put somebody on a p. 2 y. 12. Ticalgrelor. You're balancing the ischemic risk versus the bleeding risk. All these agents cause bleeding. That's how they work.

1279
03:59:53.190 --> 04:00:06.319
W. Frank Peacock: And so you use them in patients who have a high risk of thrombosis to justify the risk you take on with bleeding. That's

generally most commonly patients who've had an mi, or have a stent in their heart, because they'll clot that off.

1280
04:00:06.480 --> 04:00:15.449
W. Frank Peacock: and they would have a second mi and die. So it's the risk of death from your thrombotic risk versus the potential for complications from bleeding.

1281
04:00:16.070 --> 04:00:24.500
W. Frank Peacock: Ticagrelor is recommended by all the Major Cardiology guidelines. You can see those on the Left American Heart Association, Stroke Association.

1282
04:00:24.620 --> 04:00:28.129
W. Frank Peacock: American College of Cardiology and Sky next slide.

1283
04:00:31.140 --> 04:00:36.240
W. Frank Peacock: so that large amount of colored ball in the middle is an activated platelet.

1284
04:00:36.420 --> 04:00:43.910
W. Frank Peacock: They can be activated a number of ways and Adp is one of the big ones. That's those purple balls representing that and the P. 2, white

1285
04:00:44.290 --> 04:00:47.780
W. Frank Peacock: 12 receptor are those brown colored cones

1286
04:00:48.200 --> 04:00:54.070
W. Frank Peacock: on the top. So what happens is adp hits the receptor, and the platelet becomes activated and starts to bind other platelets.

1287
04:00:54.740 --> 04:00:56.080
W. Frank Peacock: That's how you get a clot.

1288
04:00:56.410 --> 04:01:05.030
W. Frank Peacock: Ticargoloids, represented by those blue balls can bind to the receptor and prevent adp from working. So the platelet is essentially paralyzed.

1289
04:01:05.550 --> 04:01:11.590
W. Frank Peacock: and the Bentrasumab is that purple red set of tubes.

1290
04:01:11.890 --> 04:01:17.460
W. Frank Peacock: and they bind to ticagular. So they take ticagular out of the equation.

1291
04:01:17.670 --> 04:01:30.090
W. Frank Peacock: And one of the unique things about ticagular is. It's reversible. A lot of the things that bind platelets, the platelets paralyze for life. You don't get a recovery. You have to build a new platelet. The advantage of ticagular is, it comes off the receptor. The platelet can now work again.

1292
04:01:30.280 --> 04:01:36.820
W. Frank Peacock: and that's what Ventrazumab does is it binds up the Ticagrelor, so that it no longer is available for the platelet.

1293
04:01:37.150 --> 04:01:44.340
W. Frank Peacock: and the chemical advantage is, it's about a hundred times more affinity for Adp

1294
04:01:44.650 --> 04:01:53.769
W. Frank Peacock: than sorry for Ticagrelor than the platelet receptor. So it is a giant sponge that sucks up the Ticagrelor next slide.

1295
04:01:56.820 --> 04:02:09.650
W. Frank Peacock: So the reverse. It. Trial is the FDA submission pivotal trial for Ventrazumab, and it's an open label, single arm trial. And and people say, Well, it's open label. Why don't you have a control group? And here's the ethics of that.

1296
04:02:09.800 --> 04:02:22.649
W. Frank Peacock: You got a guy who might be bleeding to death, and you say you want to be in a trial. You might get placebo, or you might get the agent, we think, might work, and nobody will ever want to be in the trial where they might get a placebo that will, the effects of which will not work, and then they will die.

1297
04:02:22.940 --> 04:02:30.120

W. Frank Peacock: So this is an open label trial 31 sites 9 countries. It will wind up here on February 10, th

1298
04:02:30.590 --> 04:02:34.029
W. Frank Peacock: and that at which point the FDA will make its decision.

1299
04:02:34.330 --> 04:02:50.999
W. Frank Peacock: The way you get in this trial is, you provide informed consent. This is the purple thing on the left that says screening. If they meet the inclusion criteria, they are then tested to make sure that they have the platelet effects of the Ticagrelor on board, because given to somebody without the platelet effects would have no benefit at all.

1300
04:02:51.170 --> 04:02:54.120
W. Frank Peacock: And it you couldn't tell the endpoint on your trial.

1301
04:02:54.510 --> 04:03:00.629
W. Frank Peacock: and then the next few days they have verify. Now, which is the platelet reactants measurement.

1302
04:03:00.900 --> 04:03:05.750
W. Frank Peacock: They get the Pk study of Ventrazumab tecagrulor.

1303
04:03:05.870 --> 04:03:34.769
W. Frank Peacock: They got all the central lab data, hemostasis data as well as anti-drug antibody data. And that's done. Day 1, 3, and at 7, and then 35 days. Outcomes were performed by central adjudication. To make sure that inclusion criteria met, and hemostasis and throthy biotic events were evaluated. The primary endpoint was achievement of ticragular reversal at 4 h of administration of entrazumab

1304
04:03:34.880 --> 04:04:00.770
W. Frank Peacock: and the primary hemostasis endpoint was, did they make hemostasis, and that was defined by 2 criteria, the gusto criteria and the connolly criteria gusto is in for populations of patients having invasive procedures. Caths and surgery and Connolly is for patients who are having spontaneous bleeding. They're remarkably similar, but they were validated in 2 different populations. So that's how we got there next slide.

1305

04:04:03.320 --> 04:04:15.639
W. Frank Peacock: And these are the people enrolled in the trial. You can see the majority of them 136 were in the Surgery group. The major bleeding group is 44 ages. The Median age is about 67.

1306
04:04:15.820 --> 04:04:28.260
W. Frank Peacock: They're predominantly white. That was a function of the countries they were done in. The major bleeding group has slightly more patients with renal disease. And that's because that's the population that has spontaneous bleeding.

1307
04:04:28.460 --> 04:04:34.790
W. Frank Peacock: Most common reason for being on Ticagrelor was Nmi in the surgical group.

1308
04:04:34.930 --> 04:04:43.310
W. Frank Peacock: and there were slightly more people getting pericutaneous intervention in the major bleeding group, or had it by history next slide.

1309
04:04:46.830 --> 04:04:50.650
W. Frank Peacock: And these are the outcomes the

1310
04:04:51.810 --> 04:05:00.290
W. Frank Peacock: at the 4 h, so that you can see the pre-dose inhibition. The completely reactance units is 50 on that 1st

1311
04:05:00.460 --> 04:05:04.670
W. Frank Peacock: block, their total enrolled population and the minimum change

1312
04:05:04.810 --> 04:05:09.830
W. Frank Peacock: and percent inhibition of Pru went down by 71%. So that's a net change of a hundred.

1313
04:05:09.830 --> 04:05:11.000
Catherine Bernstein: Minutes remaining.

1314
04:05:11.870 --> 04:05:21.159
W. Frank Peacock: And that's the same in either group. So it makes the 4 h primary endpoint of antiplatelet

1315
04:05:21.480 --> 04:05:24.119
W. Frank Peacock: effect reversal. So. But

1316
04:05:24.300 --> 04:05:33.350
W. Frank Peacock: Trasomab was very effective by 4 h of having the reversal, and this occurred within the 1st 5 min of administration of the drug next slide.

1317
04:05:36.580 --> 04:05:54.859
W. Frank Peacock: And this is the hemostasis outcomes. You can see that the proportion of making the pre-specified hemostasis criteria was 95%. So 100% of the people in surgery and about 80% of patients with major bleeding achieved the pre-specified definition of hemostasis next slide.

1318
04:05:58.180 --> 04:06:16.950
W. Frank Peacock: And these are the safety endpoints. So patients who received Ventrazumab were then categorized by this. There was no treatment. Merchant essays considered related to ventracumab. There were no teas when the outcome of death considered related to ventracumab, and the safety results were consistent with that reported in all the prior studies.

1319
04:06:17.190 --> 04:06:22.799
W. Frank Peacock: The patients who did have Ventrazumab related teas, and there are very few of them

1320
04:06:22.990 --> 04:06:34.090
W. Frank Peacock: tended to be injection, site, discomfort, and that was like in 3 patients. So next slide, so summary

1321
04:06:34.350 --> 04:06:56.390
W. Frank Peacock: current management, Ticula related. Bleeding is suboptimal. And that's just a politically correct statement, because the current management is we don't have any management. There is no other reversal agent, so we do standard of care, and we hope it works. And if you need surgery the next 2 days we're going to take our best shot. But we don't have a reversal agent currently, and this would represent a major change in our armamentarium. It would allow

1322
04:06:56.540 --> 04:07:10.590

W. Frank Peacock: providers to have different set of choices than we currently do right now. We have to balance higher bleeding versus and non-deverable patients, whether the surgery is worth it or not. At this, if we had the reversal agent we could administer the drug, and at that point you would

1323
04:07:10.890 --> 04:07:16.650
W. Frank Peacock: be able to do your surgery, and as soon as they're hemostatic afterward you could re administer the drug.

1324
04:07:16.650 --> 04:07:17.720
Catherine Bernstein: Minute, remaining.

1325
04:07:17.930 --> 04:07:20.309
W. Frank Peacock: Which are things that we can't do at the current.

1326
04:07:20.730 --> 04:07:34.389
W. Frank Peacock: They could be on Tycargalore for their platelet innovation right up to the surgery at which point you administer the reversal agent. They can have their surgery. So it minimizes the period of thrombosis risk that they currently have to have.

1327
04:07:34.840 --> 04:07:37.940
W. Frank Peacock: And so this overall represents a better management option.

1328
04:07:38.090 --> 04:07:55.650
W. Frank Peacock: So if Ventrasom has a new anticipated standard of care, the risk-benefit profile in Ticagrelor patients will be enhanced by supporting out of a hemostasis improvement and management of major bleeding, or by improved risk, mitigation, and non-deferral surgery, or invasive procedures. When a washout period is not feasible or desirable.

1329
04:07:55.800 --> 04:08:00.509
W. Frank Peacock: and with that I thank you for the opportunity to present, and I'd love to answer questions.

1330
04:08:02.420 --> 04:08:07.609
Drew Kasper: Very well, thank you for your presentation, and we'll start with questions from the public.

1331
04:08:09.460 --> 04:08:11.429
Drew Kasper: We have any questions from the public.

1332
04:08:11.570 --> 04:08:17.309
Drew Kasper: There are no questions in the Q. And a. And no raised hands.

1333
04:08:18.780 --> 04:08:41.160
Drew Kasper: There are no new questions that would be in the new tech mailbox. And so with that we'll broaden the group to my colleagues at Cms. And those of you at Cms that want to unmute, feel free to chime in with questions, and the public can continue to ask questions in the QA. Or through use of the raise hand feature. Thanks.

1334
04:08:42.940 --> 04:08:54.440
Andrew Wang: Thank you so much for your presentation. I had a few questions for you. Wanted to ask. How did you? How do you objectively determine that washout is not an option.

1335
04:08:54.800 --> 04:08:58.440
Andrew Wang: and what is the timeframe for the indicated use of ventriximab.

1336
04:08:59.210 --> 04:09:21.380
W. Frank Peacock: Yeah, that's decisions made by the surgeon at the bedside. And there are clearly times when you can wash out. So you're going to have your elective hip replacement. You can turn off the drug and wait for 5 days and go to the or the challenge with that. If you are on. If you got a stent. Those 5 days represent a risk period for you, because you might have an Mi during the 5 days waiting for your hip replacement. And that's not really the population who

1337
04:09:21.630 --> 04:09:37.709
W. Frank Peacock: got enrolled in this trial. So this trial was people who were having an Mi. And we got to go to the or today. You need a Cath now, or you're going to die, or you know you got hit by a bus, and your spleen is ruptured, and we've got to go. Take care of that, because

1338
04:09:37.930 --> 04:10:07.609
W. Frank Peacock: and those are the non, the easy ones to say we can't wait. And then there's judgment calls like appendicitis. It's not a

very big incision, you know. It's 4 inches long, and you can put compression on it, and maybe you delay for a day or 2 where you give them antibiotics, and then you do the surgery so ultimately to answer your question. There is no published guidelines on what is absolutely. You have to go to the or or not. There are ones that we believe that you need to go to the or that'd be heart attacks and major vascular surgery and intracranial hemorrhage and that sort of thing.

1339
04:10:07.790 --> 04:10:12.159
W. Frank Peacock: and there are ones that we absolutely don't have to. And in the middle there's a big gray zone.

1340
04:10:15.350 --> 04:10:28.990
Andrew Wang: Thank you so much. Are there any other outcome measures such as patient clinical outcomes, such as reduction in thermosis events, or reduced length of stay that can be attributed to Pentriximab.

1341
04:10:29.710 --> 04:10:38.969
W. Frank Peacock: Yeah. So you've you've just seen the results of the only trial so far, so I can't give you length to stay, and I'd love to tell you. Icu days are shortened and patients were discharged earlier and all that stuff.

1342
04:10:39.060 --> 04:11:06.729
W. Frank Peacock: But we're looking at a trial with less than 200 patients in it. So it's just not very big, and the variation the trial is enormous, because some of these people have are just sick. You know, they have major bleeding, and some of them aren't so bad, and it's difficult to, with true scientific accuracy, tell you that this is going to be a length of stay now I believe it will be. I just can't prove it yet, because it's not been on once. It's been on the market for a while. We'll start a registry.

1343
04:11:06.790 --> 04:11:10.859
W. Frank Peacock: and you know, in the 1st 500 patients will have a much better idea about that.

1344
04:11:13.490 --> 04:11:19.889
Andrew Wang: Thanks so much. My last question is, how was hemostasis measured in the reverse? It trial.

1345
04:11:20.830 --> 04:11:36.619

W. Frank Peacock: Sure. So hemostasis is defined on the surgical patients with the gusto criteria. And that's do. You have a bleed in a major organ like your head? Did you drop your hemoglobin by a couple grams? Were you hemodynamically unstable? Did you need a transfusion?

1346
04:11:36.720 --> 04:12:05.490
W. Frank Peacock: And so that's the people who go to the or and the Connolly trial. It's the same type of stuff. It's hemodynamically significant patients who are unstable, requiring a transfusion. But the difference is in those 2 scales is one is for surgical, that's gusto, and one is for the major bleeding that was not surgical. And the interesting thing about the major bleed. It's not surgical. Sometimes you can't even see the bleeding like a retroperitone hematoma you can't tell is even there, but the pressure is 70, and their hemoglobin is dropping. That's a major bleed.

1347
04:12:05.890 --> 04:12:11.140
W. Frank Peacock: So that's the 2. And the absence of that occurring was the primary endpoint.

1348
04:12:11.440 --> 04:12:32.879
W. Frank Peacock: So you got the ventracumab, and you no longer dropped your hemoglobin. You didn't have an additional intracranial hemorrhage. You didn't have the need for a transfusion, so that was how hemostasis was defined, and we have a clinical Endpoint Committee who evaluated all the data at hand. The physician who's at the bedside evaluated the clinical Endpoint

1349
04:12:32.940 --> 04:12:48.660
W. Frank Peacock: committee also evaluated it blinded to each other, and those results were remarkably consistent. Across the board there was one or 2 cases where they didn't agree, but it was like only one or 2. It was not, you know, of all the almost 200 cases they almost always agree.

1350
04:12:49.190 --> 04:12:51.889
W. Frank Peacock: So that's how the hemostasis endpoint was determined.

1351
04:12:54.030 --> 04:12:56.650
Andrew Wang: Thank you so much for your answers. Nothing.

1352
04:13:04.220 --> 04:13:07.139

Drew Kasper: There any other questions from Cms. Or for the public.

1353
04:13:07.640 --> 04:13:25.639
Adina Hersko: Hi, I just have one question talked about using Ventrazumab when you know there's like a 5 day period where you have to wait. But it's my understanding that after 24 h you can use platelets to some degree of efficacy.

1354
04:13:25.770 --> 04:13:36.940
Adina Hersko: So in the trial, when you're looking at the patients to include, I mean, could any of those patients have waited, let's say, one day, and compared to use of platelets versus Ventrazumab.

1355
04:13:37.780 --> 04:14:07.240
W. Frank Peacock: No, these patients. This is, you know, a prospective trial. So it wasn't randomized. But these patients who were enrolled they would get the Mentrazumab as quickly as possible, because these people had major bleeding events or were going to the or and it was not a population where you wanted to wait on the cohort you're talking about is somebody who's got unstable angina, and maybe think, well, we can wait a few days to have their multivessel disease and go to cabbage, and that's a different cohort than we enrolled.

1356
04:14:07.340 --> 04:14:19.329
W. Frank Peacock: None of these people were really felt to be safe or desirable to have their interventions delayed 24 h to see if we could get by with just platelets tomorrow. That wasn't included in this cohort.

1357
04:14:20.090 --> 04:14:20.730
Adina Hersko: Thank you.

1358
04:14:29.060 --> 04:14:31.499
Drew Kasper: Don't see any questions in the chat.

1359
04:14:32.910 --> 04:14:35.440
Drew Kasper: and there are no hands raised.

1360
04:14:37.810 --> 04:14:42.609
Drew Kasper: no questions in the new tech mailbox. Last call for questions.

1361
04:14:45.670 --> 04:14:52.169
Drew Kasper: Okay. Well, thanks again for your presentation, and we will now

1362
04:14:52.980 --> 04:14:59.699
Drew Kasper: we will now move on to hear from speakers presenting for intelliseep test.

1363
04:15:00.400 --> 04:15:03.229
Drew Kasper: You may now unmute and introduce yourself.

1364
04:15:04.190 --> 04:15:18.940
Hollis O'Neal: Hello, thank you. I'm Dr. Hollis O'neill. I'm a pulmonary and critical care physician, associate, professor of Medicine down at Lsu in Baton Rouge, Louisiana and the Medical Director of Research for our hospital here, our Lady Lake Regional Medical Center. You can go on to the next slide

1365
04:15:19.940 --> 04:15:36.219
Hollis O'Neal: here to tell you about the intelliseep test, which is a diagnostic for sepsis, as many of you know, sepsis is the most common, costly, and deadly condition facing us hospitals. It's also a time sensitive medical emergency, with up to an 8% increase in mortality for every hour of treatment, delay.

1366
04:15:36.270 --> 04:15:50.410
Hollis O'Neal: and unlike other time, sensitive conditions that present to the emergency department. Like heart attack and stroke, there is to date no rapid diagnostic that's existed to assist providers in risk stratification of these patients.

1367
04:15:50.610 --> 04:16:06.280
Hollis O'Neal: This is important because sepsis is a very difficult diagnosis, as my Ed colleagues tell me, sepsis look like a lot of looks like a lot of things, and a lot of things look like sepsis. When patients with sepsis walk through the doors of the emergency department go on to the next next slide.

1368
04:16:08.060 --> 04:16:35.070
Hollis O'Neal: The intelliseep test is a rapid diagnostic that examines the biologic cause of sepsis by quantifying the structural changes that white cells undergo upon activation enabled by recent

advances in imaging microfluidics and machine learning. This is a laboratory-based test that uses just 1 10th of a CC. Of whole blood from a purple top tube and returns results. In about 8 min you can go into the next slide.

1369
04:16:37.350 --> 04:17:02.130
Hollis O'Neal: Intelliseep provides substantial clinical improvement in Ed workflow and patient outcomes. It meets criterion 2, because it provides a clear indicator of sepsis risk in just 8 min, and it meets criterion 3. Because it enables providers to shorten the length of stay, improve resource, utilization, and most importantly, it reduces the mortality of patients who present to the emergency department with signs and symptoms of infection.

1370
04:17:03.060 --> 04:17:04.220
Hollis O'Neal: Next slide

1371
04:17:05.820 --> 04:17:28.939
Hollis O'Neal: intelliseep meets criterion 2. By providing the ability to diagnose sepsis earlier. It does this by helping providers identify patients in whom sepsis is unlikely. It allows for earlier, more informed antibiotic decisions, and it provides actionable results sooner than current methods of diagnosing sepsis. Next slide

1372
04:17:34.610 --> 04:17:43.070
Hollis O'Neal: intelliseep can achieve these objectives through a test that sorts patients into 3 interpretation bands from low to high probability of sepsis

1373
04:17:43.090 --> 04:18:11.730
Hollis O'Neal: while existing methods can take hours, or even days, and telecept generates this new information. In only 8 min. Providers can then use this information to inform rapid decisions, to treat high-risk patients aggressively, or to look for alternative causes of the presentation in low risk patients and be aware that some of these alternative diagnosis are in and of themselves, life threatening conditions that can be missed if there is diagnostic anchoring on the sepsis pathway

1374
04:18:12.380 --> 04:18:13.600
Hollis O'Neal: next slide.

1375
04:18:16.130 --> 04:18:25.879

Hollis O'Neal: In addition, the test allows providers to more accurately detect sepsis by outperforming current sepsis diagnostics and other biomarkers

1376
04:18:26.230 --> 04:18:27.360
Hollis O'Neal: next slide

1377
04:18:32.100 --> 04:18:53.220
Hollis O'Neal: existing detection focuses on symptoms of the systemic inflammatory response syndrome, or what we call the service criteria and on blood cultures. However, these 2 sepsis detection methods lack the sensitivity or specificity needed, and thus leads providers to miss the diagnosis of sepsis in some patients while providing unnecessary treatment in others.

1378
04:18:54.000 --> 04:18:55.180
Hollis O'Neal: Next slide

1379
04:18:57.350 --> 04:19:15.149
Hollis O'Neal: intelliseep exhibits diagnostic performance for sepsis comparable to that of Ekg and troponin. In the rapid diagnosis of the acute coronary syndromes. These are tests that are commonly used for another life-threatening condition, and again, intelliseep provides comparable diagnostic performance to those

1380
04:19:15.790 --> 04:19:16.870
Hollis O'Neal: next slide.

1381
04:19:20.660 --> 04:19:30.570
Hollis O'Neal: Intelliseep allows centers to significantly improve clinical outcomes by allowing providers to treat high risk patients faster than previously done.

1382
04:19:30.940 --> 04:19:32.200
Hollis O'Neal: Next slide.

1383
04:19:35.410 --> 04:20:00.219
Hollis O'Neal: Now, to give you a little bit of information on real world use, we implemented intelliseep in our medical center back in August of 2023, a little bit of background information on our Medical Center. We are the largest inpatient facility in the State of Louisiana. We're a level one trauma center with 900 beds. We see

greater than 70,000 Ed visits annually. Importantly, baton Rouge is a very diverse community, with a great

1384
04:20:00.220 --> 04:20:10.639
Hollis O'Neal: greater than 55% black or African American, and also about one in 4 patients below the poverty line, and we serve as the safety net hospital for this area.

1385
04:20:11.150 --> 04:20:12.330
Hollis O'Neal: Next slide.

1386
04:20:13.950 --> 04:20:32.190
Hollis O'Neal: We've tested over 7,000 patients since going live, and our process begins at triage with a nurse-driven order in patients who screen positive upon receiving the result. Providers act on intelliseep informed pathways for the treatment of these patients.

1387
04:20:33.440 --> 04:20:34.620
Hollis O'Neal: Next slide

1388
04:20:36.620 --> 04:20:46.680
Hollis O'Neal: the triage process results in about 10% of patients being in the waiting room when this result comes back and is received by the pro is received by the providers.

1389
04:20:46.680 --> 04:21:07.050
Hollis O'Neal: though the care team originally thought that these patients were low risk. That's why they were sent back to the waiting room. The intelliseep test highlights that about one in 5 of these patients, or 20% of them is actually high risk. And this allows us to expedite care to these patients and maximize the chances of a successful treatment in these patients who present with what we call occult sepsis.

1390
04:21:07.570 --> 04:21:08.879
Hollis O'Neal: Next slide

1391
04:21:11.170 --> 04:21:27.690
Hollis O'Neal: and telecept informed pathways, allow us to reduce unnecessary testing and associated risks. The use of this test has also resulted in more patients being discharged from the emergency department to home, and shortens the length of stay among those tested

and aided in their appropriate use of antibiotics, and others

1392
04:21:29.020 --> 04:21:30.180
Hollis O'Neal: next slide

1393
04:21:32.430 --> 04:21:48.209
Hollis O'Neal: and telecept informed care has reduced the length of stay by more than one day. It's reduced the delivery of broad spectrum Iv antibiotics by 15% and reduced blood culture utilization by 19%. This leads to less risk for the patient and lower costs for our healthcare system.

1394
04:21:48.480 --> 04:21:49.630
Hollis O'Neal: Next slide.

1395
04:21:52.400 --> 04:22:00.150
Hollis O'Neal: Lastly, and most importantly, intelliseep can aid clinicians in the delivery of care that can reduce the mortality of tested patients

1396
04:22:00.900 --> 04:22:02.080
Hollis O'Neal: next slide.

1397
04:22:04.110 --> 04:22:23.039
Hollis O'Neal: You can see here that since implementation, we have observed a 30% reduction in our observed relative risk of sepsis mortality for us, this results in approximately one life saved every week, and this is looking at pre implementation versus post implementation of both and expected deaths.

1398
04:22:23.420 --> 04:22:24.590
Hollis O'Neal: Next slide

1399
04:22:27.420 --> 04:22:37.540
Hollis O'Neal: in summary intelise that provides substantial clinical improvement by allowing more rapid and effective diagnosis of patients and allowing care that substantially improves clinical outcomes.

1400
04:22:38.320 --> 04:22:39.520
Hollis O'Neal: Next slide

1401
04:22:41.090 --> 04:22:58.250
Hollis O'Neal: just to put kind of a human face. On these results I want to introduce one of our patients, Miss Terry White. She is a patient at my facility, who benefited from the use of this test. She was initially considered low risk for sepsis, and she was one of those patients who was in the waiting room when her intelliseep result came back.

1402
04:22:58.250 --> 04:23:14.770
Hollis O'Neal: She came back as a high risk result. This alerted providers to a potentially serious infection that we're able to quickly address following detection. We're proud to have been able to treat Terry so quickly, and she had a very good outcome from a potentially disastrous condition.

1403
04:23:14.820 --> 04:23:18.829
Hollis O'Neal: I appreciate your attention, and we'll take any questions that you might have.

1404
04:23:22.400 --> 04:23:25.000
Drew Kasper: Thanks very much for your presentation.

1405
04:23:27.290 --> 04:23:32.320
Drew Kasper: and so we will start with questions from the public.

1406
04:23:36.060 --> 04:23:40.510
Drew Kasper: Don't have any questions in the Q. And a I don't see any raised hands.

1407
04:23:42.590 --> 04:23:44.040
Drew Kasper: And

1408
04:23:48.175 --> 04:23:49.779
Drew Kasper: let's see here.

1409
04:23:53.577 --> 04:23:57.619
Drew Kasper: There are no questions currently in the

1410
04:23:58.560 --> 04:24:11.619
Drew Kasper: and tap mailbox. Okay, we have one related to the Town

Hall, but it's not about this presentation, so we will open it up then to Cms. And I'll I'll start us off there

1411
04:24:13.330 --> 04:24:19.509
Drew Kasper: if the if anyone from the public has questions, though please do chime in into the Q. And a. Or with a raised hand.

1412
04:24:20.690 --> 04:24:27.469
Drew Kasper: So I wanted to ask regarding the study on the impact of Sepsis Associated mortality.

1413
04:24:27.810 --> 04:24:44.139
Drew Kasper: Is there any information available on the patient demographics or the statistical methods and results for the study? I know it's it's not yet published. Last I heard, but just wondering if there might be some more details like that available that you could share.

1414
04:24:44.490 --> 04:25:04.240
Hollis O'Neal: Sure. So those mortality data that I showed you are actually what's reported reported to our quality database viziant. So those are actually reported directly from our hospital. Certainly that that demographic you can find there. But we are, as I said, in a community that is about 55% black or African American in our

1415
04:25:04.240 --> 04:25:16.640
Hollis O'Neal: racial kind of breakdown across our patients looks very similar to our community. So you know, right at half of our patients are black or African American, and again, about 25% at or below the poverty line.

1416
04:25:17.910 --> 04:25:25.650
Hollis O'Neal: as we, you know, kind of collate more and more of these data and publish it. We can get more details of the exact demographics of those patients.

1417
04:25:26.460 --> 04:25:27.640
Drew Kasper: Oh, okay.

1418
04:25:28.750 --> 04:25:40.130
Drew Kasper: great, yeah. And and certainly any any statistical aspects of the results. Confidence intervals, or anything like that,

you know, that is available would be helpful.

1419
04:25:41.630 --> 04:25:52.560
Drew Kasper: Is there any evidence available that compares intelliseep to other sepsis screening technologies, such as the early sepsis indicator measurement for monocyte distribution width.

1420
04:25:53.280 --> 04:26:21.239
Hollis O'Neal: So there is an abstract that was done not by us, but was done at the University of Kansas, and it was published at a meeting that looked as a very small study that, compared to Mdw. Mdw. Is proprietary, and you have to be in a lab that actually has it. We don't have it in our facility and none of the facilities that we are currently in have it. We have published data recently published data

1421
04:26:21.240 --> 04:26:33.050
Hollis O'Neal: in the journal, academic emergency medicine of a pooled analysis that we did, that looks at intelise that performance against other commonly used biomarkers that are out there, including Procalcitonin.

1422
04:26:39.010 --> 04:26:45.280
Drew Kasper: It any chance sepsicite rapid would be in that no great.

1423
04:26:45.280 --> 04:26:50.920
Hollis O'Neal: So again, that's another proprietary test that, you know, is only available in certain institutions.

1424
04:26:54.410 --> 04:27:04.059
Drew Kasper: When you say it's only available whether it's the Mdw. Or subsite rapid that it's only available in certain institutions. Is that to say just that.

1425
04:27:04.380 --> 04:27:06.359
Drew Kasper: It's it's available

1426
04:27:07.180 --> 04:27:15.770
Drew Kasper: for purchase it. Just that, you know, different hospitals could could purchase it. But it's just not something that was available during your testing or.

1427

04:27:15.770 --> 04:27:16.550
Hollis O'Neal: Correct.

1428
04:27:17.270 --> 04:27:18.439
Drew Kasper: Okay. Good.

1429
04:27:19.390 --> 04:27:26.009
Adina Hersko: And to follow up on that is your technology available at other centers? Or is it just at your hospital.

1430
04:27:26.160 --> 04:27:39.520
Hollis O'Neal: It's at our hospital. It's it's across our hospital system, which is a hospital system in Louisiana and Mississippi and there's also Freighter Hospital at Medical College, Wisconsin, Milwaukee, is currently using.

1431
04:27:40.750 --> 04:27:46.690
Adina Hersko: But there's no comparison of your test as compared to any of them here tests on the market.

1432
04:27:47.300 --> 04:27:54.589
Hollis O'Neal: Direct comparison to Mdw. Other than the abstract that I told you about. No direct comparison to Septicite Rapid. No.

1433
04:27:58.050 --> 04:27:58.869
Adina Hersko: Thank you.

1434
04:28:00.660 --> 04:28:05.434
Drew Kasper: Okay, yeah, I think we'd be interested in seeing anything like that, like the one that you mentioned.

1435
04:28:06.940 --> 04:28:09.439
Drew Kasper: with the comparison against the Mdw.

1436
04:28:12.900 --> 04:28:15.170
Hollis O'Neal: Certainly we can. We can see if we can.

1437
04:28:15.270 --> 04:28:16.970
Hollis O'Neal: We can get that abstract for you.

1438
04:28:22.180 --> 04:28:27.379
Drew Kasper: Anyone else from Cms. Or the public have any additional questions.

1439
04:28:28.530 --> 04:28:30.680
Drew Kasper: I don't see any in the Q. And a.

1440
04:28:31.180 --> 04:28:33.120
Drew Kasper: There are no raised hands

1441
04:28:33.970 --> 04:28:38.989
Drew Kasper: and no new questions in the new tech mailbox. So I'll do a last call for questions.

1442
04:28:42.880 --> 04:28:45.800
Drew Kasper: Great? Well, thank you very much for your presentation.

1443
04:28:46.620 --> 04:28:47.650
Hollis O'Neal: All right. Thank you.

1444
04:28:48.910 --> 04:28:59.609
Drew Kasper: And we will now move along for the presenters up next for, or Lumen, otherwise known as Isliprost.

1445
04:28:59.780 --> 04:29:02.969
Drew Kasper: You may now unmute and introduce yourself.

1446
04:29:04.740 --> 04:29:07.110
Ken Zafren: Hi! My name's Ken Zafrin. I'm a

1447
04:29:07.350 --> 04:29:16.189
Ken Zafren: clinical professor and attending physician at Stanford, and also an attending physician in the emergency department at the Alaska Native Medical Center.

1448
04:29:17.460 --> 04:29:22.100
Ken Zafren: Thank you for the opportunity to present this information. Next slide, please.

1449
04:29:24.040 --> 04:29:34.669
Ken Zafren: I have 2 disclosures. I'm the author of the Frostbite topic, and up to date, for which I receive royalties, and I'm also consultant and advisor to serve pharmaceuticals

1450
04:29:35.670 --> 04:29:36.969
Ken Zafren: next slide, please.

1451
04:29:38.790 --> 04:29:45.059
Ken Zafren: We're going to be talking about arlumen, which is illaprossed injection for intravenous use.

1452
04:29:45.200 --> 04:29:50.559
Ken Zafren: It's the 1st and only drug therapy approved in the United States for the treatment of frostbite.

1453
04:29:50.980 --> 04:29:56.429
Ken Zafren: and the indications are severe frostbite to reduce the risk of digit amputation.

1454
04:29:57.440 --> 04:30:05.970
Ken Zafren: The there's no mortality to frostbite, but morbidity can be very severe.

1455
04:30:06.260 --> 04:30:09.019
Ken Zafren: For example, if you don't have any fingers.

1456
04:30:09.230 --> 04:30:11.880
Ken Zafren: Someone else is going to be buttoning your shirt every day.

1457
04:30:13.300 --> 04:30:22.370
Ken Zafren: Yeah, outside the United States the intravenous formulation of illipros has been available for over 30 years.

1458
04:30:22.480 --> 04:30:29.490
Ken Zafren: and the 1st published report of the use of illiprosse for frostbite was in 1994,

1459

04:30:30.870 --> 04:30:32.199
Ken Zafren: next slide, please.

1460
04:30:35.060 --> 04:30:46.260
Ken Zafren: So this slide, says frostbite, is a thermal injury caused when tissue is exposed to freezing temperatures, I think we should be a little more clear. Frostbite is freezing of the tissue.

1461
04:30:46.550 --> 04:30:50.320
Ken Zafren: There are actually ice crystals in the tissue, in someone who has frostbite.

1462
04:30:50.810 --> 04:30:53.809
Ken Zafren: It's mostly a disease of urban settings.

1463
04:30:54.210 --> 04:31:03.180
Ken Zafren: Yeah, in the modern era in the United States, and it certainly is

1464
04:31:04.150 --> 04:31:09.449
Ken Zafren: a disease that affects people with, yeah, comorbidities. Yeah.

1465
04:31:11.270 --> 04:31:16.160
Ken Zafren: the overall incidence of frostbite injury in the United States is is quite low.

1466
04:31:16.310 --> 04:31:23.979
Ken Zafren: Yeah, 62 cases. Yeah, over of Medicare claims.

1467
04:31:24.450 --> 04:31:31.830
Ken Zafren: Yeah, so quite quite a low incidence. Quite a rare disease. Next slide, please.

1468
04:31:35.330 --> 04:31:38.780
Ken Zafren: There are several classification systems

1469
04:31:39.120 --> 04:31:44.859
Ken Zafren: for frostbite, of which the 1st 2 on this slide really aren't used or useful.

1470
04:31:45.350 --> 04:31:53.489
Ken Zafren: and the last one is the one I'll discuss. It was developed by Dr. Emmanuel Cauchy from Chamonix, France.

1471
04:31:53.820 --> 04:32:05.089
Ken Zafren: and the grading system predicts tissue amputation based on the appearance of frostbitten usually hands or feet

1472
04:32:05.830 --> 04:32:14.220
Ken Zafren: after rewarming and and body temperature or slightly warmer water. So that's the initial treatment of frostbite that

1473
04:32:14.450 --> 04:32:20.609
Ken Zafren: presents to the emergency department that has not been thought already.

1474
04:32:21.750 --> 04:32:28.679
Ken Zafren: Yeah, grade one and grade 2 have no or minimal tissue loss in grade 2. It's usually loss of a nail

1475
04:32:28.920 --> 04:32:30.530
Ken Zafren: or something similar.

1476
04:32:30.760 --> 04:32:37.790
Ken Zafren: And again, these are prediction of tissue loss without the use of iliprost.

1477
04:32:39.250 --> 04:32:43.380
Ken Zafren: Yeah, the grade one. There's no cyanosis

1478
04:32:43.560 --> 04:32:47.520
Ken Zafren: grade, 2 shows cyanosis just over the distal phalanx.

1479
04:32:47.770 --> 04:32:57.300
Ken Zafren: and unless there's some question about whether it's grade 2 or grade. 3. Illiprost is not indicated for grades, one and 2

1480
04:32:57.730 --> 04:32:59.130

Ken Zafren: for grade, 3.

1481
04:32:59.300 --> 04:33:09.400
Ken Zafren: The cyanosis goes to the metacarpophalangeal joint, or just distal to the metacarpophalangeal joint

1482
04:33:09.610 --> 04:33:16.569
Ken Zafren: and the risk of tissue loss with bone amputation is about two-thirds. That's again without the use of illaprost

1483
04:33:17.220 --> 04:33:23.980
Ken Zafren: and proximal to the metacarpophalangeal joint. The risk of bone amputation is a hundred percent.

1484
04:33:24.480 --> 04:33:25.770
Ken Zafren: Next slide, please.

1485
04:33:28.980 --> 04:33:37.200
Ken Zafren: So arlumin, which is illaprost injectable, is a prostacycling memetic.

1486
04:33:37.360 --> 04:33:45.420
Ken Zafren: It that seems to work by enhancing skin blood flow, and also inhibiting the aggregation of platelets.

1487
04:33:46.099 --> 04:33:53.559
Ken Zafren: Again, it was 1st published as a use for frostbite in 1994, with 5 patients. Next slide, please.

1488
04:33:57.779 --> 04:34:01.509
Ken Zafren: The treatment regimen is pretty simple.

1489
04:34:01.860 --> 04:34:09.700
Ken Zafren: Starting low, going up to 2 nanograms per kilogram per minute. If the patient tolerates it.

1490
04:34:09.849 --> 04:34:12.720
Ken Zafren: the basic theory is to get as much of

1491

04:34:13.029 --> 04:34:16.500
Ken Zafren: the yellow prostan is possible for the best results.

1492
04:34:16.890 --> 04:34:22.090
Ken Zafren: and the doses are usually well tolerated with the main

1493
04:34:22.390 --> 04:34:27.750
Ken Zafren: adverse event being hypotension. At that point the illoprost

1494
04:34:27.869 --> 04:34:30.159
Ken Zafren: has stopped and restarted at a lower

1495
04:34:30.759 --> 04:34:34.670
Ken Zafren: dose where there wasn't hypotension next slide, please.

1496
04:34:38.020 --> 04:34:44.849
Ken Zafren: So the FDA approval is based on the only randomized, controlled style that was ever completed for frostbite.

1497
04:34:45.300 --> 04:34:49.699
Ken Zafren: It was a randomized, controlled, open label study.

1498
04:34:50.090 --> 04:34:57.740
Ken Zafren: Again in Chamonix there were 47 patients, and the control arm

1499
04:34:58.360 --> 04:35:07.709
Ken Zafren: included treatment with a medicine called buffalo metal, which is a vasodilator. In fact, all of the treatment arms included booth flow metal.

1500
04:35:08.160 --> 04:35:14.240
Ken Zafren: And then there were 2 non-control arms, illoprossed

1501
04:35:14.810 --> 04:35:19.360
Ken Zafren: and illoprost plus recombinant tissue plasminogen activator

1502

04:35:19.770 --> 04:35:28.779
Ken Zafren: and the primary efficacy endpoint was number of patients with amputation predicted by bone scan after 8 days of treatment

1503
04:35:30.570 --> 04:35:31.920
Ken Zafren: next slide, please.

1504
04:35:34.970 --> 04:35:37.890
Ken Zafren: So the results were quite amazing.

1505
04:35:38.169 --> 04:35:41.859
Ken Zafren: In the illaprossed group grade 3 and grade 4

1506
04:35:42.310 --> 04:35:45.580
Ken Zafren: frostbite patients who were the only patients in the study.

1507
04:35:45.919 --> 04:35:46.779
Ken Zafren: Yeah.

1508
04:35:47.689 --> 04:35:59.939
Ken Zafren: Had 0 amputations, the combined iliprost and recombinant Tpa, yeah, group had very few amputations.

1509
04:36:00.340 --> 04:36:05.669
Ken Zafren: It's not clear exactly. Yeah. Why the number wasn't 0 there as well.

1510
04:36:05.970 --> 04:36:16.639
Ken Zafren: Yeah, although we have some possible hypotheses, such as the effects on coagulopathy by the addition of.

1511
04:36:17.210 --> 04:36:18.760
Catherine Bernstein: You have 3 min remaining.

1512
04:36:19.230 --> 04:36:21.949
Ken Zafren: Of recombinant Tpa.

1513
04:36:22.180 --> 04:36:25.359

Ken Zafren: The adverse events were minor again.

1514
04:36:25.470 --> 04:36:28.710
Ken Zafren: all related to hypotension, flushing nausea.

1515
04:36:28.840 --> 04:36:36.859
Ken Zafren: palpitations, and vomiting, and in this study there were no discontinuations because of adverse events. Next slide, please.

1516
04:36:39.890 --> 04:36:45.990
Ken Zafren: had a more recent multi-center, retrospective, observational study from Calgary.

1517
04:36:46.189 --> 04:36:50.260
Ken Zafren: Alberta, Canada shows not quite as amazing results.

1518
04:36:51.060 --> 04:36:56.919
Ken Zafren: but in the real world. Study here that the historical controls

1519
04:36:57.210 --> 04:37:01.349
Ken Zafren: had over twice the amputation rate as the the study group

1520
04:37:02.669 --> 04:37:06.280
Ken Zafren: in both grade 3 and grade 4. Frostbite next slide, please.

1521
04:37:10.029 --> 04:37:14.410
Ken Zafren: so that our lumen fulfills a significant.

1522
04:37:14.570 --> 04:37:24.809
Ken Zafren: clear, unmet medical need for an FDA approved therapy to prevent amputation of patients with severe frostbite.

1523
04:37:25.310 --> 04:37:29.510
Ken Zafren: It's been an internationally recognized treatment for many years.

1524
04:37:29.610 --> 04:37:34.190
Ken Zafren: It's finally available in the United States very

effective. It's a safe

1525
04:37:34.610 --> 04:37:42.549
Ken Zafren: drug that that really has very little in the way of adverse events. Next slide, please.

1526
04:37:43.890 --> 04:37:45.770
Ken Zafren: I'm sorry. Actually, that's the last slide.

1527
04:37:46.230 --> 04:37:48.850
Ken Zafren: Yeah. Be happy to take any questions.

1528
04:37:52.669 --> 04:37:54.901
Drew Kasper: Great. Thank you very much for your presentation.

1529
04:37:55.659 --> 04:37:59.619
Drew Kasper: and at this point we'll open it up to questions from the public.

1530
04:38:02.349 --> 04:38:10.559
Drew Kasper: I don't have questions in the QA. And I do not see any raised hands amongst the participants and attendees.

1531
04:38:12.399 --> 04:38:23.389
Drew Kasper: So let's see here no questions in the new tech mailbox, either. Okay, well, I'll start us off. Then, with questions from Cms.

1532
04:38:26.079 --> 04:38:47.239
Drew Kasper: I wanted to ask you is, I'll post anticipated to be used instead of Tpa, or in addition to, is there anything more you could say about that? You actually started to get into speaking a little bit about the the group in which both were used. Perhaps that was kind of illuminating on this topic. Even

1533
04:38:49.119 --> 04:38:55.978
Drew Kasper: wonder if there's any more you could just say about the an anticipated use of of the 2 together versus

1534
04:38:56.859 --> 04:38:59.079
Drew Kasper: I will post in singularity.

1535
04:38:59.740 --> 04:39:03.330
Ken Zafren: Now, that's a great question, and thank you for that.

1536
04:39:03.470 --> 04:39:04.570
Ken Zafren: The

1537
04:39:05.520 --> 04:39:13.450
Ken Zafren: authors of the original randomized, controlled trial theorized that there may be cases in which the patient would benefit from the use of both.

1538
04:39:13.919 --> 04:39:18.019
Ken Zafren: Yeah, the protocols that I've seen some

1539
04:39:18.630 --> 04:39:23.030
Ken Zafren: some places are planning to use both for grade 4 frostbite.

1540
04:39:23.259 --> 04:39:31.649
Ken Zafren: Yeah, other than that I'm I'm not aware of any set plans or best approach

1541
04:39:31.880 --> 04:39:34.210
Ken Zafren: at this point. We just don't have the evidence.

1542
04:39:38.400 --> 04:39:39.190
Drew Kasper: Oops.

1543
04:39:40.060 --> 04:39:46.349
Drew Kasper: And with regard to the the randomized study upon which

1544
04:39:46.730 --> 04:39:59.769
Drew Kasper: you stated the FDA approval was based, it appears that the mean age of the patients was 33.1. Could you clarify how these patients may be generalizable to the Medicare population?

1545
04:40:02.510 --> 04:40:03.850
Ken Zafren: For the

1546
04:40:04.270 --> 04:40:23.129
Ken Zafren: they're younger than the general Medicare population clearly, and have fewer comorbidities, and for the study in Calgary, just to bring that in where the results weren't quite as good. I think some of it has to do with the fact that the patients in the 1st study were mostly young.

1547
04:40:23.450 --> 04:40:32.049
Ken Zafren: healthy people, who hadn't been frozen very long and were plucked by helicopter off of the slopes of Mont Blanc in Chamonix.

1548
04:40:32.200 --> 04:40:38.640
Ken Zafren: and the Calgary study would probably have a more representative

1549
04:40:38.830 --> 04:40:49.190
Ken Zafren: population, and and these people were on the streets, so they probably weren't found as as quickly. And the other difference between those studies I should have mentioned is that the

1550
04:40:49.400 --> 04:40:56.180
Ken Zafren: Chamonix study gave the illaprosse for 8 days, and the Calgary study only for 5 days, so that might have

1551
04:40:56.390 --> 04:41:00.729
Ken Zafren: influence the the difference in mortality. I'm sorry. Morbidity.

1552
04:41:04.970 --> 04:41:09.900
Drew Kasper: Interesting thanks, and

1553
04:41:10.630 --> 04:41:15.130
Drew Kasper: I think we've got time here. I did have one more question for the sake of clarity.

1554
04:41:15.380 --> 04:41:20.859
Drew Kasper: You mentioned the Wilderness medical Society practice guidelines having recognized

1555

04:41:20.980 --> 04:41:26.719
Drew Kasper: intravenous alloprostas, the the 1st line treatment of deep or severe frostbite.

1556
04:41:27.320 --> 04:41:49.370
Drew Kasper: recognizing that these are recommendations and also that tpa and isliprost aren't necessarily mutually exclusive. In your opinion. Do the Wilderness Medical Society practice guidelines state a preference for iliprost over Tpa. Even in circumstances where Tpa can be given early after injury, where there are no clear contraindications.

1557
04:41:50.360 --> 04:41:56.129
Ken Zafren: If my memory is correct, I believe that they prefer

1558
04:41:56.550 --> 04:42:01.650
Ken Zafren: ill across in all cases, but I'd have to go back and look at the

1559
04:42:02.010 --> 04:42:06.720
Ken Zafren: the wording for practical purpose. Since Illiprost hasn't been available

1560
04:42:07.170 --> 04:42:10.050
Ken Zafren: and wasn't available in 2,019.

1561
04:42:10.160 --> 04:42:19.130
Ken Zafren: Yeah, the recommendation was for use of Tpa. But illaprosse wasn't on the table in the United States. Hope that answer your answers. Your question.

1562
04:42:21.820 --> 04:42:27.655
Drew Kasper: Yeah, yeah, I don't know if it was entirely clear in the, in, in those in those guidelines.

1563
04:42:28.460 --> 04:42:33.784
Drew Kasper: and yeah, I I recall that that piece as well. I think they had said where it's available.

1564
04:42:35.897 --> 04:42:45.489
Drew Kasper: kind of get around the fact that it wasn't yet available

in the Us. Okay, thank you.

1565
04:42:45.950 --> 04:42:49.149
Drew Kasper: I'm gonna open it up to see if others from Cms.

1566
04:42:49.700 --> 04:42:55.969
Drew Kasper: And I will take a look around and see if there's any from the public as well. But if anyone else from Cms has additional questions.

1567
04:43:01.920 --> 04:43:07.340
Drew Kasper: there are new raised hands in the Q. And A is clear

1568
04:43:10.110 --> 04:43:13.089
Drew Kasper: new questions in the new tech mailbox.

1569
04:43:15.120 --> 04:43:18.207
Drew Kasper: Okay, okay, all right. Well, thank you very much.

1570
04:43:20.270 --> 04:43:21.210
Drew Kasper: And

1571
04:43:24.390 --> 04:43:44.699
Drew Kasper: and in wrapping up and concluding our event today, just wanted to restate that comments for consideration in the Ips proposed rule related to substantial clinical improvement for criterion for Ntap, including comments on the Fy. 2026 applications, and on the Town Hall. Presentations

1572
04:43:45.100 --> 04:43:55.910
Drew Kasper: must be sent to Cms. Via email to newtek@cms.hhs.gov with the subject line town Hall comment, followed by the technology name.

1573
04:43:56.120 --> 04:44:03.530
Drew Kasper: All comments must be received by Monday, December 16, th 2024 at 5 Pm. Eastern Standard time.

1574
04:44:05.040 --> 04:44:18.500
Drew Kasper: And now I did also just want to say, thank you for all the presenters for all the time that you put into these presentations,

and for the attendees and the questions you brought to the table.

1575
04:44:18.740 --> 04:44:39.969
Drew Kasper: Also, we'd appreciate any feedback on the Town Hall, whether it's about what you think worked well or didn't work well, or how we might improve the process. We welcome any input that you have about the Town Hall, and any feedback can be sent via email to that same address, newtek@cms.hhs.gov with the subject line town Hall.

1576
04:44:40.720 --> 04:44:50.919
Drew Kasper: Thank you again to all the presenters, panelists, and attendees. We appreciate your time and preparation, and this concludes our day's event. Happy holidays to you all.

1577
04:44:51.470 --> 04:44:52.610
Drew Kasper: Take care.