Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

Office of Therapeutic Products

77th Meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee

Web Conference

November 21, 2024

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

Transcript Produced By: Translation Excellence

3300 South Parker Road, Aurora, CO 80014

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Opening Remarks: Call to Order

Dr. Ahsan: Welcome. My name is Taby Ahsan. I'm the Vice President of Cell and Gene Therapy operations at the City of Hope. Today, I am Chairing the 77th meeting of the Cellular Tissue and Gene Therapies Advisory Committee today on November 21st, 2024 for the Center for Biologics Evaluation and Research at the FDA.

The committee today will meet in open session to discuss and meet recommendations on Supplemental Biologics License Application 125586/546 from AstraZeneca to confirm the clinical benefit of andexanet for patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

I'd like to welcome the members of the committee, the members of the sponsor, the FDA, and the public that are viewing remotely. As we start going through the day, I do want to remind the committee members that if they would like to speak, have a question or a comment, that they should raise their hand in the chat feature and turn on their camera and I will call on them when we are ready to hear their comments.

Administrative Announcements

So, with that, I hand it over to Cicely Reese, the Designated Federal Officer for today's meeting, to make administrative announcements, conduct roll call, and read the conflict of interest statement.

Dr.. Reese: Thank you, Dr. Ahsan. Good morning, everyone. I am Cicely Reese, and it is my honor to serve as the Designated Federal Officer for today's Cellular Tissue and Gene Therapies Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, and the committee, I am happy to welcome everyone for today's virtual meeting. Next slide, please.

At this time, I would like to acknowledge and thank my Division Director in the Division of Scientific Advisors and Consultants, Dr. Prabhakara Atreya, and my team, whose contributions have been critical for preparing for today's meeting. Those persons include Ms. Tonica Burke and Ms. Joanna Malsch, as well as many others from the Division who have provided helpful administrative support in preparation for this meeting. Next slide, please.

I would now like to acknowledge CBER leadership, including Dr. Peter Marks, the Director of CBER, and Dr. Celia Whitten, Deputy Director of CBER, Dr. Nicole Verdun, Super Office Director of CBER's Office of Therapeutic Products, OTP, and many other OTP staff who will be serving as speakers and presenters during the day, as indicated on the agenda. On behalf of DSAC, our sincere gratitude also goes to many CBER and FDA staff working very hard behind the scenes to ensure that today's virtual meeting will also be a successful one.

I also thank all other FDA staff contributing to today's meeting, some of whom are present and others who may be joining the meeting at other times. Next slide, please.

Please direct any press or media questions for today's meeting to FDA's Office of Media Affairs at fdaoma@fda.hhs.gov.

I would also like to thank the audiovisual team, Mr. Gideon McMullin, Mr. Sheldon Thwaites, and Mr. Derek Bonner for facilitating the meeting today. The transcriptionist for today's meeting is Ms. Catherine Diaz.

Roll Call

We will begin today's meeting by taking a formal roll call for the committee members and temporary members. When it is your turn, please make sure your video camera is on and you are unmuted. Then state your first and last name, organization, expertise, or role. And when

finished, you may turn your camera off so we may proceed to the next person. Please see the member roster slides in which we will begin with the chairperson. Next slide, please.

Dr. Ahsan, please go ahead and introduce yourself. Thank you.

Dr, Ahsan: Thank you, Cicely. My name is Taby Ahsan. I'm the Vice President of Cell and Therapy Operations at the City of Hope. I am also head of the Center for Bio-innovation and Manufacturing. My expertise is as a bioengineer. I'm focused on stem cells, tissue engineering, immune-effector cell therapies, and have recently become more involved in viral vector manufacturing.

Dr.. Reese: Thank you, Dr. Ahsan. Next slide, please. Ms. Eggiman, you may be on mute. Ann-Virginie, you may be on mute. We can come back and she can introduce herself. We'll move on to Dr. Donald Kohn, and then we'll go. Dr. London, you can continue from there.

Dr. Kohn: Thank you. Good morning. I'm Donald Kohn. I'm at the University of California, Los Angeles. I'm a pediatric bone marrow transplant physician, and I do clinical and preclinical research on stem cell gene therapy.

Dr.. Reese: Dr. London?

Dr. London: Good morning. Wendy London from Dana-Farber Boston Children's Cancer and Blood Disorder Center. I'm a professor of pediatrics in Farber Medical School and a biostatistician. My expertise is in the conduct of phase 1, 2, and 3 clinical trials, and my research interest is in the identification and utilization of prognostic factors to assign treatment in neuroblastoma.

Dr.. Reese: Thank you. We'll circle back and see if Ann-Virginie Eggiman is ready.

Ms.. Eggimann: Hi. Good morning. I'm Ann-Virginie Eggiman. I am Chief Regulatory Officer at Tessera Therapeutics. I will be the Industry Representative for this advisory committee today. Thank you. Thank you. Next slide, please.

We'll begin with Dr. Lund. I think, Dr. Lund, we may be waiting on him, so we'll go on to Dr. Morrison.

Dr. Morrison: I'm Sean Morrison. I direct Children's Research Institute at the University of Texas Southwestern Medical Center. My expertise is in the area of stem cells and cancer, particularly hematopoietic stem cells and hematolysis.

Dr.. Reese: Thank you. And I've been informed that Dr. Lund is here. If you can go ahead. Thank you.

Dr. Lund: Sure. My name is Troy Lund. I'm at the University of Minnesota, Pediatric Bone Marrow Transplant. My expertise is in preclinical modeling of hematopoietic stem cell transplant and involved with numerous gene therapies to treat pediatric rare diseases. Thank you.

Dr.. Reese: Thank you. Kathleen?

Dr. O'Sullivan-Fortin: Hi. I'm Kathleen O'Sullivan-Fortin. I am the sitting Consumer Representative for today's meeting. I am a co-founder of ALD Connect, an organization for a rare neurodegenerative disease.

Dr.. Reese: Thank you. Next slide, please. Dr. Ott?

Dr Ott: Hello, everybody. My name is Melanie Ott. I direct the Gladstone Institute of Virology. I'm also a professor of medicine at UCSF. My expertise is in various viruses, cell biology, and in viral vectors.

Dr.. Reese: Thank you. Dr. Snyder?

Dr Snyder: I don't see my picture. Hi. I'm Evan Snyder. I'm a professor at the Sanford Burnham Prebys Medical Discovery Institute and UCSD in La Jolla. I'm director of the Center for Stem Cells and Regenerative Medicine. Obviously, I'm a stem cell biologist, but with a particular expertise in the nervous system and also the lung. I'm also a pediatric neurologist and a newborn intensivist neonatologist.

Dr.. Reese: Thank you. Dr. Tifft?

Dr. Tifft: Good morning. My name is Cynthia Tifft. I'm the Deputy Clinical Director at the National Human Genome Research Institute at the NIH in Bethesda, Maryland. My expertise is in pediatrics, medical genetics, and gene therapy specifically for lysosomal storage diseases and the sphingolipidosis..

Dr.. Reese: Thank you Next slide, please. Dr. Wolfe?

Dr. Wolfe: Good morning. Gil Wolfe. I'm a SUNY distinguished professor at University of Buffalo in the Department of Neurology. I'm the immediate Past Chair and the current Chief of Service as well. My main interest clinically and research-wise is neuromuscular medicine. I still do care for patients with intracranial bleeds, although I do try to transfer them to our stroke service when that occurs, but it occurred as recently as yesterday afternoon.

I'm on service right now.

Dr.. Reese: Thank you, Dr. Wolfe. Dr. Wu?

Dr. Wu: Good morning. My name is Joe Wu. I'm a professor of medicine and director of the Stanford Cardiovascular Institute. I am a cardiologist. I see patients with heart diseases. My research expertise is in cardiac cell tissue and gene therapy going from basic to translation to clinical trials.

Dr.. Reese: Thank you. Next, we will do a roll call for our temporary voting members, starting with Dr. Sanjay Ahuja. Thank you.

Dr. Ahuja: Hi. Good morning. My name is Sanjay Ahuja. I'm a Pediatric Hematologist with expertise in bleeding and clotting disorders in children and young adults. I am the Chief Medical Officer at Indiana Hemophilia and Thrombosis Center, part of Innovative Hematology. Thank you.

Dr.. Reese: Thank you. Dr. Kindzelski?

Dr. Kindzelski : Yes. Good morning. Andrei Kindzelski. I am a Chief Translational Research Branch, Blood Division, the National Heart, Lung, and Blood Institute, NIH, expertise benign hematology, thrombosis, and hemostasis. Thank you.

Dr.. Reese: Thank you. Dr. Koroshetz?

Dr. Koroshetz: I am Walter Koroshetz. I'm the director of the National Institute of Neurological Disorders and Stroke. And prior to coming to NIH, I was an internist and neurointensivist at Mass General Hospital.

Dr.. Reese: Thank you very much. Next slide, please. And we'll begin with Mr. Joseph O'Brien.

Dr. O’Brien: Hi. This is Joe O'Brien. I'm president and CEO of the National Scoliosis Foundation. I am the Patient Representative who is also personally experienced with atrial fibrillation, atrial flutter for over two decades. I'm an Eliquis patient who has had cardiac tamponade, several catheter ablations, and cardioversions in surgeries, and a GI bleed.

Dr.. Reese: Thank you. Dr. Ortel?

Dr. Ortel: Hi. I'm Tom Ortel from Duke University. I am the Chief of Hematology, and my particular clinical and research interest is in thrombotic disorders, as well as in thrombotic therapies.

Dr.. Reese: Thank you. And last but not least, Dr. Ratan?

Dr. Ratan: Yes. Good morning, everybody. I'm Raj Ratan. I'm the CEO of the Burke Neurological Institute and a professor at Weill Cornell Medicine. I am a neurologist with training in neurorehabilitation, and I am also a molecular and cellular neuroscientist with a particular interest in preclinical models of brain hemorrhage, specifically involving cell death and repair.

Dr.. Reese: Thank you, everyone. There are a total of 18 participants, 17 voting members, and one non-voting member. Thank you all for your introductions. Next slide, please.

Before I begin reading the Conflict of Interest statement, I would like to briefly mention a few housekeeping items related to today's virtual meeting format. For members, speakers, FDA staff, and anyone else joining us in the Zoom room, please keep yourself on mute unless you are speaking to minimize feedback.

If you have your hand raised and are called upon to speak by the chairperson, please turn your camera on, unmute, state your name, and speak slowly and clearly, so that your comments are accurately recorded for the transcription and captioning. Thank you.

Conflict of Interest Statement

I will now proceed with reading the Conflict of Interest statement for the public record. The Food and Drug Administration, FDA, is convening virtually today, November 21st, 2024, for the 77th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee, also called CTGTAC, under the authority of the Federal Advisory Committee Act, or FACA, of 1972. Dr. Taby Ahsan is serving as the chair for today's meeting.

The committee will meet in open session to discuss and make recommendations on Supplemental Biologics License Application 125-586-546 for AstraZeneca to confirm clinical benefit of Andexxa, coagulation factor Xa recombinant, and activated ZHZO for patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The topic is determined to be a particular matter involving specific parties. PMISP.

With the exception of the Industry Representative member, all standing and temporary voting members of the CTGTAC are appointed as special government employees and regular government employees from their other federal agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws include, but are not limited to, 18 U.S.C. Section 208, which is being provided to participants in today's meeting and to the public. Related to the discussions at this meeting, all members and RGE and SGE consultants of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouse or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements or CRADAs, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation. FDA has determined that all members of this advisory committee, both regular and temporary members, are in compliance with federal ethics and conflicts of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts of interest when it is determined that the agency's need for a special government employee's services outweighs the potential for a conflict of interest created by the financial interest involved, or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by committee members and consultants, there have been no conflict of interest waivers issued under 18 U.S.C. Section 208 in connection with this meeting. We have the following consultants serving as temporary voting members, Dr. Sanjay Ahuja, Dr. Andrei Kindzelski, Dr. Walter Koroshetz, and Mr. Joseph O'Brien.

Introduction of Committee

Ms. Kathleen O'Sullivan-Fortin is serving as the Consumer Representative for this committee meeting. Consumer Representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee.

We have one Patient Representative, Mr. Joseph O'Brien. Patient representatives are special government employees and are screened and cleared prior to their participation in the meeting. They are temporary voting members of the committee.

Ms. Anne-Virginie Eggimann will serve as the Industry Representative for today's meeting. Industry Representatives are not appointed as special government employees and serve as non-voting members of the committee. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the committee.

FDA encourages all meeting participants, including Open Public Hearing speakers, to advise the committee of any financial relationships that they may have with any affected firms, its products, and, if known, its direct competitors. We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFL and exclude themselves from such discussions, and their exclusion will be noted for the record. This concludes my reading of the conflict of interest statement for the public record.

At this time, I would like to hand the meeting back over to Dr. Taby Ahsan. Thank you.

Dr. Ahsan: Thank you, Cicely, for all that administrative effort. I want to take a moment at this point to thank the members, the standing members of the committee, the temporary members, the sponsors, and the FDA representatives. It takes a lot of time and effort to prepare for this meeting, and I appreciate everyone's effort in that regard.

Today, it's going to be a long day. There's going to be a lot of work to do, so I appreciate, again, the focus and the energy that goes into this important day as we move forward. We're going to start with an FDA introduction. For that, I'd like to introduce Dr. Nicole Verdun. She is the Super Office Director of the Office of Therapeutic Products, known as OTP, in CBER of the FDA. Dr. Verdun..

FDA Introductory Remarks: Nicole Verdun, M.D.

Dr. Verdun: Thank you. Thank you for that introduction. On behalf of the FDA, we would like to welcome you to the 77th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee. We really do appreciate and advance the discussion and attention to this meeting and the engagement from all participants, including the patients and caregivers that we all serve.

The purpose of the meeting today is to discuss and obtain input on the benefit risk profile of andexanet, which is indicated for the treatment of patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. This product was granted accelerated approval based on a surrogate endpoint of decrease in anti-Xa activity in healthy volunteers. We are also here to discuss the increased risk of thrombosis observed with andexanet for the proposed indication in the context of the clinical efficacy that was shown in ANEXXA-1, which is the trial that we will be discussing today.

This application was submitted for conversion, and we will be discussing some of the data that was submitted in the context of these questions around the benefit risk profile. We will start today with presentations from the applicant, followed by those from FDA, followed by an open public hearing and discussion. Thank you in advance for your engagement and input on this important topic, and I would like to turn it back over to our chair.

Dr. Ahsan: Thank you, Dr. Verdun, for providing all that context for the day. That's very helpful as we start to navigate our way through this. We're going to start, as she mentioned, with the applicant presentations.

There's a series of speakers from the applicant. I ask that the first speaker then introduce the second, the second, and the third, and then so on. Starting us off will be Jeffy John, who is the Director of Regulatory Affairs at AstraZeneca Biopharmaceuticals.

Mr. John, if you could turn on your camera.

Applicant Presentations: Jeffy John M.B.A

Dr. John: Good morning. My name is Jeffy John, Director of Regulatory Affairs at AstraZeneca.

Thank you to the chair, the committee, and the FDA for the opportunity to present data supporting indexing, which safely and effectively reverses the anticoagulation effects of direct factor Xa inhibitors, restores hemostasis, and stops bleeding in patients who experience life-threatening or uncontrolled bleeds. The evidence we will present today supports conversion to full approval for andexanet's currently approved indication and posology. Factor Xa inhibitors have become the new standard of care for anticoagulation.

Millions of Americans depend on these medications to prevent blood clots, but they also put patients at significant risk for an acute life-threatening bleed. In these critical bleeding situations, there is a need for specific reversal agents that effectively restore physiologic coagulation. ANDEXXA, which we will refer to as andexanet, received accelerated approval in 2018.

This was based on a high unmet medical need and clinical evidence demonstrating rapid, reversal of factor Xa inhibition. Currently, the andexanet is only therapy approved for this purpose. Thus, it's an important component in the bundle of care emergency physicians use to rapidly reverse factor Xa inhibitors and manage uncontrolled life-threatening bleedings.

Andexanet is a recombinant inactivated analog of human factor X that sequesters factor Xa inhibitors. It acts as a decoy receptor that recognizes and binds directly to these inhibitors with high infinity. Since it cannot form a prothrombinase complex, it lacks the procoagulant activity of native activated factor Xa.

Through this action, andexanet rapidly reduces free plasma concentration of factor Xa inhibitors. This neutralizes their anticoagulant effect. Since andexanet is a protein, it's not metabolized by race or ethnicity dependent routes such as cytochrome P450s.

In addition, neither race nor ethnicity affects andexanet's affinity for factor Xa inhibitors. Our clinical development program includes four studies that support andexanet benefit-risk. Our first

in human studies, ANEXXA-A and ANEXXA-R, clearly demonstrated that andexanet rapidly reduces anti-factor Xa activity and restores thrombin generation.

These data are from ANEXXA A. Anti-factor Xa activity is on the left and thrombin generation is on the right. Among healthy volunteers treated with apixaban, andexanet reduced anti-factor Xa activity by 92% and also restored thrombin generation within two minutes following administration. Consistent evidence from both studies confirmed the mechanism of action and set the foundation for our clinical development program.

Next came ANEXXA-4. This study looked at hemostatic benefit in a relevant patient population. It also confirmed andexanet's ability to rapidly reverse factor Xa inhibitor activity. These studies supported accelerated approval.

We then initiated ANNEXA-I as a post-marketing requirement at the request of the FDA and other regulatory authorities. ANNEXA-I achieved its primary endpoint and demonstrated superiority to usual care. The results confirmed the hemostatic benefit of andexanet and demonstrated an acceptable and consistent safety profile in the context of a life-threatening, uncontrolled bleed.

FDA's post-marketing requirement included several key design factors, including enrolling at least 440 patients to verify the hemostatic effect of andexanet, assessments at 12 hours post-randomization with a 30-day safety follow-up period, and a blinded adjudication committee to determine hemostatic efficacy. ANNEXA-I was designed to fill regulatory requirements globally.

Thus, patients treated with rivaroxaban, apixaban, or edoxaban were enrolled, in line with approvals outside the U.S. Today, we will share results from the pre-specified primary analysis

population, as well as the FDA-requested sensitivity analyses of patients receiving apixaban or rivaroxaban. These sensitivity analyses demonstrate consistent evidence of efficacy and safety.

Let me take a few moments now to provide some context on FDA's comments on the primary endpoint. The original protocol met the key criteria specified in the PMR, which I described a few moments ago. The protocol was designed and intended to convert accelerated approval to traditional approval based on hemostatic efficacy at 12 hours. This endpoint was agreed upon with the FDA division.

The first patient was enrolled in 2019. In 2020, we submitted a protocol amendment that added neurological functional assessments at 24 hours as secondary endpoints. This was intended to provide reasonable measures of effect of andexanet on early neurological function.

The FDA review division consulted with the division of neurology products on this matter. Since the proposed secondary endpoints were neurological, not hematology-based, feedback from the neurology division indicated that these functional assessments at 24 hours are potentially meaningful in the setting of ICH, but that the most important measures of neurological functional assessments should be later, at 90 days.

The sponsor considered this feedback, but decided to continue with the original study design aligned to the 2018 PMR for hemostatic efficacy. Neurological assessments at 24 hours were therefore added as exploratory endpoints, and the length of study follow-up continued to be through 30 days.

In summary, ANNEXA-I demonstrates a positive benefit-risk profile for andexanet, and meets the post-marketing requirement, supporting conversion to full approval. For patients on oral factor Xa inhibitors facing life-threatening bleeds, andexanet meets a clear medical need for an effective reversal agent.

ANNEXA-I demonstrated that andexanet provides both statistically significant and clinically meaningful improvements in hemostatic efficacy, compared to usual care, by rapidly reversing the anticoagulant effect of factor Xa inhibitors in critical bleeding situations.

There was an increased risk of thrombotic events. As you will hear in our presentation, for patients presenting to the ICU with a life-threatening ICH, multiple simultaneous treatments are implemented to stop the bleed and reduce the risk of brain injury.

While thrombotic events can occur, critical care teams are well-equipped to manage this risk in the ICU setting. No new safety signals or adverse drug reactions were seen in ANNEXA-I. Therefore, consistent with previous studies, ANNEXA-I supports an acceptable safety profile in the setting of a life-threatening bleed. Based on these results, our proposed indication is the same as the one for accelerated approval.

ANDEXX A is indicated for patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Here now is the agenda for the rest of our presentation. We have additional experts with us to help address your questions.

All outside experts have been compensated for their time and travel. Thank you. I'll now turn the presentation to Dr. Nyquist.

Burden of Life Threatening Bleeds Related to FXa, Inhibitors and Need for Effective Reversal Agents

Dr. Nyquist: Good morning. Thank you, I'm Paul Nyquist, Professor of Neurology, Anesthesia, Critical Care medicine, Neurosurgery, and General Internal Medicine at Johns Hopkins. I'm here to describe what happens when patients experience life-threatening bleeding while taking a factor Xa inhibitor and the need for immediate, effective anticoagulation reversal in this setting.

Factor Xa inhibitors are the standard of care for anticoagulation and the treatment of atrial fibrillation and venous thromboembolism. They've revolutionized the care of these patients, as major medical organizations recommend their use for these indications.

In 2022, 4.8 million Medicare patients in the U.S. received a factor Xa inhibitor and their use continues to rise. Of these, three to five percent will experience a major bleeding requiring hospitalization. These bleeds occur across various body sites and are classified into four categories as shown here.

Bleeding causes of hospitalization are GI, intracranial, and trauma-related bleeds. Now specifically focusing on ICH as the director of the Neurocritical Care Unit at Johns Hopkins, I routinely care for patients experiencing these life-threatening events. In this setting, rapid intervention is key to reduce injury and improve survival.

Our goal is clear. We must immediately stop the bleed. To achieve this goal, critical care teams employ a rapid bundle of care.

This consists of multiple fast-acting interventions done simultaneously and swiftly to stabilize the patient and control the bleed. Therefore, it is essential to have specific, potent, and fast-acting anticoagulant reversal agents. It's important to note that effective anticoagulant reversal exposes patients to their underlying thrombotic risk. For ICH, this risk is also heightened by the bleed itself which increases thrombosis. Emergency and critical care teams are fully equipped to manage these complications. In fact, once we achieve hemostasis, minimizing thrombotic risks is a critical aspect of early secondary prevention.

For example, venous thrombotic complications are handled per AHA guidelines by a lower-dose anticoagulation prophylaxis, typically initiated within 24 to 48-hour(inaudible).

We always want to restart anticoagulant therapy as soon as possible to mitigate the risks of venous thrombotic complications and arterial thrombotic risks. In the setting of ICH, our primary treatment goal is to reduce hematoma expansion, which represents a well-established predictor of clinical outcome.

Hemostasis is not achieved, the risk of neurologic deterioration, worsening functional outcomes, and death rises significantly with every passing minute. In fact, evidence shows for every one mL increase in hematoma volume, the patient's risk of death or severe neurologic dependency increases by 5%. Therefore, rapidly limiting hematoma expansion is crucial for improving patient outcomes.

Patients with a factor Xa associate ICH have a significant risk of mortality. In fact, studies consistently demonstrate in-hospital mortality rates between 23 and 27%. In addition to pivotal clinical trials, evaluating chronic treatment factor Xa inhibitors show mortality rates exceeding more than 45% after an intracranial hemorrhage. andexanet is the only approved factor Xa-specific reversal agent for patients treated with apixaban and rivaroxaban, who experience these life-threatening bleeds. Four-factor PCC is only approved for warfarin reversal. It doesn't rapidly reverse the anticoagulation effects of factor Xa inhibitors.

It's important to note that all of these reversal agents were approved based on laboratory coagulation parameters, measurements of hemostatic efficacy for the standard in the industry. Since andexanet receives accelerated approval, multiple clinical practice guidelines have recommended its use for reversing anticoagulation with life-threatening bleeding situations.

ICH setting factor Xa inhibitor use requires immediate action. Time is brain. Rapid treatment is critical to reduce brain injury. In this setting, multiple treatments and care processes are administered in the ICU. These are guided by treatment protocols to outline how to

implement the bundle of care treatment approach. The immediate goal of care is to stop the bleed with andexanet Patient is stable. Protocols are in place to identify and treat the thrombotic events.

In summary, patients need effective anticoagulation reversal to rapidly restore hemostasis and to stop the bleeding. Timely intervention is crucial to prevent complications. There is a critical need for specific anticoagulation reversal agents in the setting of life-threatening bleeding. Andexanet offers a targeted solution. For these reasons, it is vital component of the bundle of care used by hospitals around the country to rapidly reverse anticoagulation with factor Xa inhibitors and effectively manage uncontrolled life-threatening bleeding events.

Thank you. I will now turn the presentation over to Dr. Ladenvall.

Andexanet Efficacy: Per Ladenvall, M.D., Ph.D.

Dr Ladenvall: Thank you and good morning. My name is Per Ladenvall, Global Clinical Head at AstraZeneca. I'm a cardiologist with a research interest in thrombosis, hemostasis, and stroke for more than 20 years. I will present clinical data demonstrating that andexanet rapidly reverses the anticoagulation effects of factor Xa inhibitors, restores hemostasis, and stops bleeding in patients who experience life-threatening or uncontrolled bleeding.

ANNEXA-I was a randomized open-label multi-center phase 4 study in patients receiving direct oral factor Xa inhibitors presenting with an acute infusible bleeding exome. Patients were randomized one-to-one to receive either andexanet or usual care. Patients randomized to and andexanet received one of two dosing regimens based on the acute pathology.

The comparator of usual care was defined as any treatment other than andexanet with the majority of patients receiving four-factor PCC. Imaging evaluations were performed based on 12

hours following randomization. Neurological assessments were conducted at baseline and repeated up until 72 hours covering the acute phase of ICH.

Following treatment, patients were followed for 30 days to assess safety events. The primary efficacy endpoint was assessed by three components covering different aspects of effective hemostasis. To achieve effective hemostasis, patients had to meet all three criteria, no hematoma expansion above 35%, no neurological deterioration, and no use of rescue therapy.

ANNEXA-I included an interim analysis after 50% of the estimated total sample size of 900 patients was adjudicated for the primary endpoint. The data cutoff for the interim analysis is represented in the primary efficacy population. Cleaned interim data were presented to the data safety monitoring board. The DSMB recommended to stop the study as the efficacy criteria had been met. Because of this, we will present results from the primary efficacy population as well as the extended population. Baseline demographics were balanced between treatment groups. Mean age was 80 years. 54% were male and the majority were white. Approximately 88% of patients were enrolled in Europe.

Baseline disease characteristics were also balanced between treatment groups. Approximately 60% of patients received apixaban and 29% of patients received rivaroxaban. Baseline hematoma volume was 10.6 milliliter in the andexanet group and 9 milliliters in the usual care group. Baseline clinical characteristics were also balanced between treatment groups and reflective of the patient populations with an increased thrombotic risk, (inaudible) , and decoagulation. Turning now to the efficacy results. ANNEXA-I demonstrated that andexanet is superior to usual care in achieving effective hemostasis at 12 hours post-randomization.

67% of patients in the andexanet group compared to 53% of patients in the usual care group achieved the primary endpoint. The absolute treatment difference of 13.4% was

statistically significant with a p-value of 0.003. Looking specifically at the subset of patients receiving apixaban or rivaroxaban, the most commonly used factor Xa inhibitors and those that are included in the andexanet USPI, we also see a consistent hemostatic benefit with andexanet. This treatment effect was generally consistent across predefined subgroups based on demographic and important baseline characteristics.

Minimizing hematoma expansion is a clinically meaningful outcome in the setting of life-threatening ICH. This benefit is supported by consistent efficacy favoring andexanet across all components of the primary endpoint, including hematoma expansion, neurological deterioration, and use of rescue therapy.

Finally, andexanet's rapid reversal is also illustrated by the secondary endpoint. Andexanet was superior to usual care in reducing anti-Factor Xa activity from baseline to nadir during the first two hours post-randemization with a 94 median reduction in the andexanet group compared to a 27 median reduction in usual care group.

In conclusion, andexanet is superior in reversing the anticoagulant effects as shown by the reduction in the anti-Factor Xa activity and provides superior hemostatic efficacy in patients with life-threatening bleedings compared to usual care. Andexanet provided numerical improvements in all aspects of effective hemostasis.

Data from both the ANNEXA-I and ANNEXA-4 demonstrate the hemostatic benefits of andexanet in patients treated with Factor Xa inhibitors who experience life-threatening or uncontrolled bleeding. Andexanet should therefore be considered as a critical component of the bundle of care to control the bleeding in these emergency situations. And with that, I would like to hand over the presentation to my colleague, Dr. Rohit Narayan.

Andexanet Safety: Rohit Narayan, M.B.Ch.B.

Dr. Narayan: Thank you, Dr. Ladenvall. My name is Rohit Narayan, Patient Safety Physician at AstraZeneca. I will now review the data from ANNEXA-I that demonstrate a consistent safety profile of andexanet in a setting of uncontrolled and life-threatening bleeding.

Andexanet has a well-established safety profile. This is supported by multiple studies that have included 553 healthy volunteers and a total of 741 patients with life-threatening bleeding, including those from both ANNEXA-4 and ANNEXA-I. Since approval in May 2018, andexanet has been used worldwide in more than 70,000 patients, with over 36,000 treated in the United States. Based on the totality of evidence from clinical trials and post-marketing experience, no new safety signals have been identified.

Today, I will focus on the safety data from ANNEXA-I. Overall, most patients in both study groups experienced a treatment-emergent adverse event. Treatment-emergent serious adverse events were higher in the andexanet group. Treatment-emergent adverse events leading to death occurred in 24% of patients on andexanet versus 20% on usual care, with 74 deaths for all-cause mortality in andexanet and 70 in usual care.

It's important to point out that not all deaths were recorded as adverse events leading to death. Early hematoma expansion or intracerebral bleeding and associated neurological deterioration were recorded as outcomes reflecting disease progression. The mortality rates in both groups reflect the acuity and sickness of these patients.

The overall safety profile of andexanet compared to usual care is similar in the subset of patients on apixaban and rivaroxaban. Therefore, to provide a thorough assessment, I'll focus on the complete safety data from the overall population.

More patients in the andexanet group experienced the treatment-emergent serious adverse events compared to usual care. Infections such as pneumonia and nervous system disorders due to the underlying bleeding events were most common, and these complications are an expectation in a critically unwell patient in this setting. However, the difference in thrombotic events is notable for both myocardial infarction and ischemic stroke.

There were more treatment-emergent adverse events leading to death in the andexanet group than in usual care, noting that some events were exempt from adverse event reporting. In both groups, the drivers of death were the hemorrhage itself and related complications, such as pneumonia, which is common in this vulnerable hospitalized population. Presented here is the Kaplan-Meier curve of time to all-cause mortality through 30 days. Here we can see that the two curves cross several times over the 30-day period.

Overall, the mortality rate was similar between groups. Turning now to thrombotic events, which were captured as adverse events of special interest. Of note, thrombotic events are a known adverse reaction to andexanet, and the U.S. label includes a boxed warning for this risk.

Investigators in ANNEXA-I were directed to submit all potential thrombotic events for review by a blinded endpoint adjudication committee, or EAC, while events were also identified through medical review. To address FDA recommendations from ANNEXA-4, ANNEXA-I enhanced surveillance for thrombotic events, using specific terms to capture them for adjudication. The EAC followed a pre-specified charter confirming thrombotic events in 27 andexanet patients and 15 patients in the usual care group.

On the next slide, we will detail some differences between these data and the FDA review. This slide shows thrombotic events identified by the FDA review in ANNEXA-I for patients on rivaroxaban or apixaban, compared to the independent adjudication committee's

findings. The FDA noted nine additional events total in the andexanet group, and three more in the usual care group.

The blinded adjudication committee did not classify these as thrombotic events, according to the pre-specified adjudication charter. The additional events noted by the FDA does not impact the overall interpretation of the results. The adjudicated thrombotic event rates in the subset aligned with rates in the overall population. We will focus on these adjudicated events for the remainder of the safety presentation.

The proportion of patients with a thrombotic event confirmed by adjudication through 30 days post-randomization was higher in the andexanet group than in the usual care group. The rate of thrombotic events is similar to ANNEXA-4 and is reflected in the current USPI.
Among these events, there was a higher frequency of ischemic stroke and myocardial infarction in the andexanet group.

Additionally, six patients in the andexanet group and two in the usual care group had an adjudicated thrombotic event leading to death. In the andexanet group, these deaths occurred on or after day 16, except one death on day two that was confounded by presentation with multi-trauma and multiple comorbidities.

Furthermore, these patients were elderly, they were fragile, they had multiple comorbidities, and experienced complications from the index bleeding event, where these factors may have also contributed to the ultimate fatal outcome. Re-anticoagulation was not randomized in ANNEXA-I, and physicians could restart anticoagulation at their discretion. When patients received at least one dose of anticoagulation, thrombotic event rates were similar between the andexanet group and usual care group, and is similar to observations noted in ANDEXXA 4.

These data are supportive of instructions in the label, which are to resume anticoagulant therapy as soon as medically appropriate following treatment with andexanet.

Post hoc analyses of ANNEXA-I revealed numerical differences in thrombotic events in patients with a history of cardiac failure, stroke, or myocardial infarction, but did not reveal a treatment arm interaction with subgroups. These comorbidities are well known to be associated with thrombotic risk.

They are, in fact, used in assessment tools, such as CHADS-VASc score for anticoagulant decision making in non-valvular atrial fibrillation patients. Based on this data, we are proposing to update the USPI to inform physicians that patients with a history of stroke, myocardial infarction, or heart failure may face a higher thrombotic risk after treatment with andexanet.

In summary, in the setting of uncontrolled and life-threatening bleeding events, data from ANNEXA-I supports an acceptable safety profile of andexanet. The higher rate of thrombotic events is acknowledged, but it is put into a context where the patient is suffering a life-threatening bleed with an imminent risk of mortality, and it's weighed against the superior hemostatic efficacy demonstrated by andexanet when there is an urgent need to achieve hemostasis.

The USPI is proposed to be updated, informing use in specific patients with high baseline thrombotic risk. 30-day mortality rates were similar between groups, and causes of death are in line with other studies.

The safety profile of andexanet demonstrated by ANNEXA-I is concordant with the established profile and consistent with the mechanism of action. No new safety signals or adverse drug reactions were identified. Thank you. I will now turn the presentation over to Dr. Ashkan Shoamanesh.

Clinical Perspective: Ashkan Shoamanesh

Dr. Shoamanesh: Thank you, and good morning. My name is Ashkan Shoamanesh. I'm an Associate Professor of Medicine in the Department of Neurology at McMaster University in Hamilton, Canada, where I hold the Marta and Owen Boris Chair in Stroke Research and Care. I am grateful for the opportunity to share my perspective on the data presented today. The treatment of patients with ICH requires rapid decisions in emergency settings.

In the acute ICH setting, our goal is to stop the bleed and minimize the risk of hematoma expansion to increase the likelihood that the patient will survive and reduce their risk of long-term disability. In these scenarios, time is of critical importance. To put this into perspective, presented here is a patient of mine who arrived at the emergency department with an ICH.

He was taking anticoagulation as part of his maintenance medications for stroke prevention in the setting of atrial fibrillation. At the baseline scan, his hemorrhage was around 3 ml. Despite receiving non-specific reversal treatment, within 12 hours, the hematoma grew to 42 ml.

Unfortunately, he ultimately died due to complications associated with the hemorrhage. This case underscores the importance of controlling hematoma growth and why rapid specific reversal agents are essential for restoring coagulation quickly in these life-threatening scenarios.

Time is key in the management of patients experiencing an acute ICH. Here are data demonstrating the inverse exponential relationship between time from symptom onset to presentation and the probability of significant hematoma growth. The majority of hematoma expansion occurs within the first three hours after the bleed begins. In the setting of ICH, even small increases in hematoma volume substantially increase the deleterious effect that these events have on patient outcomes.

Thus, in the acute setting, there is an urgent need to ensure we have access to effective medications that rapidly minimize individual patient risk factors, including anticoagulation. I'd also like to highlight that reversing anticoagulation to minimize hematoma expansion is one aspect in the bundle of care for patients presenting with acute ICH. To help put this into perspective, here is an overview of the full care pathway at my hospital.

Before the patient arrives to the emergency room, EMS collects critical details like symptom onset, vitals, and whether anticoagulation is being used. This information, along with the patient's underlying conditions, informs us about their thrombotic and bleeding risks. Upon arrival, a CT scan determines the location and size of the hemorrhage, guiding treatment decisions.

A multi-pronged strategy of parallel treatments that is individualized to the patient ensues, with the aim of minimizing hematoma growth and ultimately safeguarding brain health.

For instance, if the hemorrhage is associated with elevated blood pressures, intensive blood pressure management becomes a priority. Equally important for the care of these patients is the reversal of coagulopathies, particularly through the use of reversal agents in patients receiving anticoagulants.

But time is of the essence because hematoma expansion occurs maximally within the first six hours of symptom onset, and the sooner the risk factors such as hypertension and coagulopathy are normalized, the greater the likelihood of preventing hematoma expansion. Rapid effective normalization of coagulation is additionally a very important prerequisite for life-saving neurosurgical procedures. Andexanet has been tailor-made for this indication and addresses a medical need for a rapid and potent reversal agent for factor Xa inhibitors.

Presented here are the results from the primary and secondary efficacy endpoints in ANNEXA-I. Andexanet demonstrates to see significant improvements in hemostatic efficacy and reductions in anti-factor Xa activity. This is clinically meaningful because our goal in treating these patients is to stop the bleeding event so that the patient survives with the least amount of disability.

So, from my perspective, there is no question whether andexanet effectively reverses the effect of factor Xa inhibitors, but is a 13.4% absolute difference in effective hemostasis clinically relevant? Well, the answer is yes. What I find most relevant about the findings from ANEXXA-I are the consistent benefits seen when evaluating hematoma growth. Presented here are the proportion of patients achieving excellent or good hemostasis.

In both cases, more andexanet-treated patients achieve these thresholds. In a setting where increases in hematoma size drive the risk of death and long-term disability, these data reflect a clinically meaningful outcome. Another aspect of the data from ANNEXA-I worth highlighting is the potential for even greater benefits in the real-world setting, where treatment initiation occurs faster than in clinical trials.

ANNEXA-I, on average, a time from baseline scan to randomization was approximately one hour. This is an arbitrary factor or artifact that is only seen in clinical trial settings. As such, in ANNEXA-I, the median door-to-needle time ranged from 2.1 to 2.3 hours.

This is much longer than what is seen in clinical practice of patients with ICH in the United States, which has been reported at less than 90 minutes in a setting of life-threatening brain bleed. Time to treatment is paramount. Therefore, from my perspective, the hemostatic benefit of andexanet-it and its ability to minimize hematoma expansion is underestimated in

ANNEXA-I due to factors that are necessary for conducting a randomized controlled study that would not be applicable to the real-world setting.

But what about safety? From my perspective, the rate of thrombotic events seen with andexanet-it in the ANNEXA-I trial is consistent with established rates reported in the literature and observations in the setting of effective reversal of anticoagulation using other agents in patients with ICH. The thrombotic risk associated with rapid reversal of factor Xa inhibitors is well-known and outlined in a box warning in the U.S. label. When evaluating this risk across two clinical studies, the safety profile remains consistent.

The risk of thrombotic events is real and clinically important. However, we must continue to remind ourselves that this risk must be put into context with the management of a life-threatening event where our primary goal is to stop the bleeding.

In the emergency or critical care setting, specific reversal agents are essential in this effort. While the risk of thrombosis may be elevated, critical care teams are well-equipped to monitor and manage these complications.

In particular, stroke neurologists are very familiar with these rapid risk-benefit analyses in the emergency setting and routinely make individualized treatment decisions. Moreover, the pivotal studies show that after stopping the bleed, we can manage the thrombotic risk by following guideline-recommended approaches to venous thromboembolism prophylaxis and restarting anticoagulation therapy, ensuring patients remain protected against their underlying conditions.

In summary, reducing hematoma expansion is the primary goal of medical interventions in the setting of acute intracranial hemorrhages. Time is brain, and we need therapies that help us

achieve this goal. Evidence from an ANNEXA-I shows that andexanet fills an important medical need as an effective rapid reversal agent for factor Xa inhibitors.

When balancing reductions in hematoma expansion versus an increase in thrombotic risk, I conclude that andexanet has positive benefit risk for patients treated with factor Xa inhibitors when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

Accordingly, I believe it would be a great disservice to our patients if andexanet was not available for consideration as part of the care pathway. Thank you. Dr. Roe will now moderate the Q&A session.

Applicant Presentation: Q & A

Dr. Roe: Hello. I'm Dr. Matthew Roe, and I'm a Cardiologist and Vice President and Head of Early CVRM clinical development at AstraZeneca. We're happy to address your questions now.

Dr. Ahsan: So I'd like to start recognizing members of the committee that have questions. Dr. Koroshetz, if you'd like to ask your question.

Dr. Koroshetz: I have a couple. I'll just start with one. So I saw what looked like an argument that using anticoagulation according to standard of care after intracerebral hemorrhage was associated with no difference in thrombotic events between the two groups.

But on the other hand, I feel I also saw that most of the thrombotic events, certainly the strokes, occurred in the first three days after hemorrhage, where that would be a problem. So I'm just wondering, maybe ask Paul Nyquist, is that even relevant here, given the fact that you're not going to really start things that soon? So anticoagulation is not going to get you too much help. Most of the thrombotic events, it looks like there within the first couple of days right after the ICH.

Dr. Roe: So I'll ask Dr. Nyquist to respond to the question as a neurocritical care intensivist, and also Dr. Spiropoulos as a coagulation expert to share his opinion on when and how to reinitiate anticoagulation.

Dr. Nyquist: Thank you for the question, Dr. Koroshetz. Let me just reiterate, you're concerned that most of the ischemic strokes occurred within the first three days, within the first day, 24 hours after the event, and how that would affect care, or whether or not it's relevant for the use of indexing that to reverse the risk.

Is that correct?

Dr. Koroshetz: Whether the argument that anticoagulation use is going to solve the problem, it seems to me that that, if they're having that early, you're not going to have people on anticoagulants. So it's not going to, doesn't really help the argument.

Dr. Nyquist: Well, according to the AHA guidelines, we would start that within the first 24 hours, just to state what the standard is right now based on guidelines. However, there's other evidence that we can start as early as 12 hours, based on data primarily looking at CT scans from hematoma stabilization. I have to agree with you, there is a possibility that it would not affect the outcomes. However, in this setting, we have patients who are severely ill, and patients who are at most highest risk of this are also the ones who are in the need of our bundle of care.

And as part of that bundle of care, we're now turning into this need for rapid hemostasis reversal in order to mitigate through newly developed techniques, such as minimally invasive surgery, established techniques for hydrocephalus treatment, and line placements. So while I think that what you're saying is possibly true, I also think that the true hypothesis has not yet been tested. Thank you.

Dr. Bravos: Good morning. My name is Alex Bravos. I'm a thrombosis expert and professor of medicine at the Zucker School of Medicine and assistant director of anticoagulation and clinical thrombosis at Northwell Health in New York.

I echo the statements of my colleague, Dr. Nyquist, and I do want to emphasize the fact that during the course of the ANNEXA-I trial, the American Heart American Stroke Association guidelines were updated to reflect the fact that early initiation of thromboprophylaxis, again within 24 to 48 hours, supported its use in the setting of ICH.

So I think this is during the course of the ANNEXA-I trial, and I think we can appreciate that both the practice guidelines as well as clinical practice were evolving during the course of the ANNEXA-I trial. The other thing that I would like to support is the fact that there are now also recent studies to suggest that there are now multiple approaches for re-anticoagulation in the setting of ICH. One can think about using a stepwise approach to therapeutic dose of anticoagulants or intermediate dose anticoagulants, especially if given during the first seven days, to mitigate serious adverse events, including thrombotic risks with the ICH.

So in summary, I think it's important to keep in mind that in a life-threatening bleed, the need for immediate and effective hemostasis outweighs any potential downstream risk of thrombosis. But as was iterated before, we now have various re-anticoagulation strategies that could be done as soon as medically possible based on an individualized and holistic approach to mitigate thrombotic risk using a bundle of care approach in this very vulnerable population.

Dr. Ahsan: Great. Thank you for that question and that response. I think we'll move on to Dr. Ott.

Dr. Ott: Yes. Hello. Thank you. Let me lower my hand. I have a question regarding the two dosages that were used in the trial, the high dose and the low dose. I wanted to know

whether that reflects current clinical practice and also whether there were differences in thrombotic events between high dose and low dose.

Dr. Roe: So I will first answer that question, then ask my colleague, Per Ladenvall, to respond to the second part of your question.

The current pathology and the dosing algorithm that was used in ANNEXA-I is shown here. And it's important to understand when we're looking at analyses of patients who received either a higher versus a low dose, those are analyses of patients eligible for that dose. These were not pre-randomization subgroups.

Now, as expected, those patients who received the high dose had a higher baseline anti-factor Xa level, as shown here, compared with those who received the low dose. In both cases, the dosing algorithm worked and rapidly reversed that anti-factor Xa activity effect.

Now I'll ask my colleague, Per Ladenvall, to describe the outcomes that you asked about relative to dosing.

Dr. Ladenvall: Thank you. And as shown by Dr. Roe, there were two treatment regimens, the high dose and the low dose regimen, which is done both in the ANNEXA-4 studies and in the ANNEXA-I study and is reflected in the currently approved label.

And therefore, that is what we are using in clinical practice. So patients in high dose and low dose, there are differences in their baseline characteristics due to this selection ahead of treatment. And what was noted in ANNEXA-I was that there was imbalances in those small subgroups where there were more patients with heart failure, patients with a higher hematoma volume, and patients with a higher diastolic blood pressure, which was not present in the similar corresponding patients in the usual care group. So, they were not present in the andexanet at low dose groups. Interestingly, similar imbalances was not observed in the prior study, ANNEXA-4.

So if we are looking at the outcomes in ANNEXA-4, we see that the outcomes we observed between the high dose and the low dose is similar and that we don't see any indications that there would be difference between the high dose and the low dose in that study where there were no imbalances in the treatment groups.

So therefore, we don't see a reason to believe that we have a difference in the outcomes between the high dose and the low dose groups.

Dr. Ahsan: Great. Thank you for the question and thank you for helping walk us through the stratified data. Dr. Ratan.

Dr. Ratan: Yeah, I have a number of questions, but I'll ask one right now. So I'm curious about whether, as you know, that interstitial hemorrhage is more common in Asians and Blacks, and it looked like your ethnic population was primarily white. I don't know if that reflects the factor Xa inhibitor population, but I wonder if you could comment on ethnicity and the relevance of your trial for different ethnic groups.

Dr. Roe: So, andexanet is a protein and it's not metabolized by routes that are known to have racial and ethnic differences. So the binding affinity is similar across racial and ethnic groups.

Additionally, population PK and PD analyses have not shown a race or ethnicity dependency, including in Asian patients. While we recognize the importance of studying diversity, it's also important to recognize that we are doing several additional studies to further analyze the use of andexanet across diverse populations.

So first is the reversal study shown here, which is an observational study conducted in four countries, including the United States, that is almost completed with recruitment of 2,000

patients to analyze how andexanet is being used in routine practice, and 27% of the patients enrolled to date are non-white.

Furthermore, we are doing a study that has finished recruitment but has not yet reported out in terms of final data, analyzing in the United States only the use of andexanet versus four-factor PCC in GI bleeding. And in this study, as you can see here, approximately 30% of the patients were Black or African American, and then 5% to 6% were Asian. So with these additional studies, we will be able to provide further perspective on the impact of andexanet across racial and ethnic groups.

Dr. Ratan: Great. There may be others who have questions. I'll come back if I have another one.

Dr. Ahsan: Yeah, if it's on a separate topic, that would be great, but I do want to make sure that your question was fully answered, Dr. Ratan, which is you think that you're…this is not my field, but that there are demographic differences in who presents, but I think the applicant was talking about physiologic differences in relation to the protein with the hope that the new continued data in the multinational studies will provide some insights. Is that accurate?

Dr. Roe: Are you asking me or are you asking Dr. Ratan? I'm sorry.

Dr. Ahsan: Well, asking Dr. Ratan if the clinical side was…if I captured that correctly, because I think this is an important point. Was that what you were referencing, Dr. Ratan?

Dr. Ratan: I think it was in part, but I think the answer covered it. It's just that the incidence of intracerebral hemorrhage in Black and Asian populations is higher, so it does seem like it would be of value to actually test in those populations, and I think as was mentioned, that they're going to be looking at that.

Dr. Ahsan: Okay, great. Thank you. We'll move on. Dr. Wu.

Dr. Wu: Yeah, so thank you so much for the great presentation. I have two quick questions. The first question is, can the sponsor kind of speculate why is it that you're seeing absolutely no statistical difference in terms of the mortality between the treatment versus the non-treatment group? And then the second interrelated question is that the anti-XA activity, you're using that as a…I guess as a biomarker, but, you know, for example, for a lot of the biomarkers, low pH, for example, is bad for diabetic ketoacidosis, but if you fix the pH with bicarbonate, it doesn't seem to help the patients.

So, I want to ask this. Do you see a correlation between your anti-XA activity correlating with hemostasis, meaning that when you lowered it with your drug, or does it correspond to better hemostatic efficacy?

Dr. Roe: So, to answer your first question on the mortality results and providing further context, I'll ask Per Ladenvall to respond. And then to answer your second question on the correlation between reduction in anti-factor Xa activity and hemostasis, I'll ask Ashkan Shoamanesh to respond with some analogies that have been done specifically to address that question.

Dr. Ladenvall: So, on the topic of mortality, as you concluded, we noted similar mortality rates between the treatment groups, and the Kaplan-Meier curve crossed several times during the 30 days. But this post-point estimate has large confidence intervals ranging from 0.78 to 1.49, indicating uncertainty on this endpoint in this trial with 500 patients. And to fully elucidate this, we would require a study which would be larger in the range of 3,000 patients.

But looking at the data from ANNEXA-I, we see that the mortality rates are between 25 and 30 percent in the trial, and there's only a fraction of the deaths that are related to hemostasis. We have the death due to the index bleeding within the first 72 hours, and we have the death due

to progression of the ICH. And, of course, we also have a few fatal thrombotic events, which is on the balance of the hemostasis.

But the majority of the events are related not only to the intracranial hemorrhages, but there's also complications such as infections that are contributing to the mortality in this hospitalized vulnerable patient population. So, the ANNEXA-I design was optimized for hemostatic efficacy, and the mortality results we observe in ANNEXA-I is reflecting ICH and its complications in this vulnerable patient population.

Dr. Shoamanesh: So, I would just like to echo that mortality is a complicated scenario, and ICH has multiple competing events. And to get beyond that noise, you would need a very large trial, and our trial was just not powered to demonstrate a difference. And the COFS interval would indicate that we could have missed the 22% reduction in mortality. Now, moving on to the next question regarding the association between anti-factor Xa activity and hematoma expansion.

Similarly, it's a multifactorial complicated process in that there are several drivers of hematoma expansion in patients with acute ICH. These include the baseline blood pressures, the presenting time from symptom onset to presentation under scan, as well as how large that hematoma is at presentation. All these factors drive the excess risk of hematoma expansion. When we adjust for these competing risk factors, we find strong relationships between anti-factor Xa activity and hematoma expansion. This is demonstrating the multivariable analysis looking at competing factors contributing to hematoma expansion. I'll drive your attention to the second row, where we see that a strong predictor of not achieving hemostatic efficacy is their baseline presenting anti-factor Xa activity.

Intuitively, the greater the amount of anticoagulation on board that is reflected by the degree of anti-factor Xa activity at baseline, the greater that person's risk was of expanding. In

addition, when we adjust for these additional factors, we see that the delta, the degree of reduction from baseline to nadir in anti-factor Xa activity was strongly correlated with hematoma expansion.

Dr. Ahsan: Great. Dr. Wu, did you get a full answer for that?

Dr. Wu: Yeah. I mean, I got a full answer, but maybe as a follow-up question, does that mean in the future you check the baseline, the patient's baseline anti-Xa activity, and then decide which patients will benefit from this drug because it's expensive drug, right? Versus which patient will not?

Dr. Roe: So to answer the question about the use of anti-factor Xa activity level testing within clinical practice, I'll ask Dr. Spyropoulos, to respond.

Dr. Hello, Yes. Alex Spyropoulos,. If I can have the anti-FXa slide up. I think it's important to note that anti-factor Xa is a good to reasonable predictor of the anti-coagulant activity of the anti-Xa DOACs, including rivaroxaban and apixaban.

And it's much akin to the use of the International Normalized Ratio, or INR, in the setting of warfarin-associated bleeding and reversal with PCC. So the paradigm is quite similar. Most coagulation experts agree that a threshold of 30 nanograms per ml is somewhat predictive, if one goes under that threshold, of a lack of clinically meaningful anti-coagulant effects in that setting.

Now, we did see, and this is data from the ANNEXA-I trial, that within one hour there was a 94% reduction in anti-factor Xa activity with andexanet that was not seen with usual care, mostly that included patients with PCCs. So I think this delta is, in my view, quite clinically meaningful, showing that, again, it is an important component with respect to hematoma expansion to reduce that anti- Xa activity. And as Dr. Shoamanesh has said, there are other

factors, including systemic blood pressure, the size of the initial hematoma, and the time of presentation that also can affect the hematoma expansion.

But I think overall, anti-factor Xa is a good marker to predict the, again, reversal effects of andexanet. I don't think it's the only marker, and it should not be used in isolation with all the other factors discussed.

Dr. Ahsan: Great. Thank you. That was an important point. The relationship between anti-factor Xa reduction and clinical benefit or benefit is a point of discussion later in the day. And I think this concept also of using it as an indicator for when to treat is an interesting one that we can also explore during the discussion that the committee will have in the afternoon.

Dr. Wolfe, if you could express your question, please. Oh, sir, you're on mute, actually.

Dr. Wolfe: Oh, there you go.

Dr. Wolfe: All right. Thanks for the presentation. So, yeah, this is a tough balance, as has been mentioned. My questions, the first two, has to do with the thrombosis issue. And the first one is, most of the patients got low dose.

It was 79%, I believe. Has there been any experience, either clinically or an investigational side of things, on using even a lower dose? Is that possibly what people might do as it expands in the clinical space pending full approval? And then the other question is, can Dr. Nyquist or anyone else speak to the resumption of anticoagulation?

So, how are lessons learned from this trial may be translating or will translate to speedier use of resuming anticoagulation to reduce that thrombosis risk? And then the third question has to do with the hemostasis primary outcome. There was a slide looking at the North American population. There did not seem to be a difference. It was a smaller N granted, but I could not sense that there was a difference between the two arms of the trial on that primary outcome.

Dr. Roe: So, thank you for the questions. To answer your first question, I'll ask my colleague, Chris Penland, to weigh in on those considerations. Then Dr. Nyquist will respond to your second question, and I will respond to your third question about North America.

Dr. Penland: Thank you, Chris Penland, Clinical Pharmacology and Pharmacometrics Program at AstraZeneca.

What I'd like to share with you is that both doses were set to reach the intended target, and what I'm sharing with you here is PKB simulations based on clinical studies in bleeding patients and healthy volunteers, but specifically in bleeding patients for a typical high-dose eligible case. And in this case, we see that the approved pathology of high-dose results in a high number of patients reaching the intended target of anti-factor Xa reversal, whereas giving a lower dose in the light blue bars results in a far fewer fraction of patients achieving that same target. This is also true of the low-dose eligible scenarios whenever they are an even lower dose, so both doses represent a minimal dose necessary to achieve a high number of patients reversed to target. Thank you.

Dr. Nyquist: Hi, I'm Paul Nyquist. Thanks for the excellent question. You know, the issue of when to resume anticoagulation and setting particular intercranial hemorrhage is a very difficult question. Most people advocate waiting at least six weeks at this time. To do a clinical trial like that would be very, very difficult because of the issue of ethics and clinical equipoise, the fact that they're complex patients, many of them have neurosurgical issues, and so forth.

So it's very hard to do that in an equal manner. However, the literature in ischemic stroke shows that beginning anticoagulation up to four days is probably close to becoming the standard of care. And I suspect that over time, based on many case series, that we'll be able to resume

anticoagulation of cranial hemorrhage much earlier, although doing a study like that would be very difficult to do at this point in time. Does that answer your question?

Dr. Wolfe: Yes.

Dr. Roe: And then to answer your question about the results in North America and in the ANNEXA-I, it was that the region was a predefined subgroup, pre-randomization subgroup, and as shown here, the treatment result for hemostatic efficacy had wide confidence intervals in North America due to the small sample size, as we know. However, it is important to recognize that the patients who were enrolled and included in North America were similar to those in Europe, as shown here.

So baseline clinical characteristics were similar between the two regions. And importantly, too, in the ANNEXA-4 trial, where a larger proportion of patients were enrolled from North America, here we see similar results of hemostatic efficacy with a much tighter confidence interval with respect to North America compared with other regions.

Dr. Wolfe: Thanks.

Dr. Roe: Thank you.

Dr. Ahsan: Great. Thank you for that thorough answer. Dr. Morrison.

Dr. Morrison: Yeah, thank you. The applicants have argued that critical care teams are well-equipped to deal with thrombosis. But in the data, my understanding is that 4% more of the andexanet treated patients experienced treatment emergent adverse events that led to death. And you just talked about the difficulty of deciding when to resume anticoagulant use. So don't the data suggest that the care teams struggle to deal with the side effect?

Dr. Roe: So I'll ask Ashkan Shoamanesh to respond as how care teams are managing this in the setting of a rapidly evolving clinical situation, because I believe your question is really related to the clinical decision-making process.

Dr. Shoamanesh: So I think the question, Ashkan Shoamanesh, the question, I think, raises important clinical matters regarding risk-benefit analysis of resuming anticoagulation in these patients and also how to manage the thrombotic events once they arise.

Certainly, as you've heard, the guidelines are going earlier and earlier in resuming prophylactic anticoagulation, even more so than was the standard in North America and Europe at the time of the conduct of the trial.

Secondly, thrombotic events leading to death needs to be taken with a grain of salt because, of course, those that have thrombotic events are sicker patients, as you've seen, those with a prior history of stroke, prior history of MI, and prior history of CHF. So the individual contribution of that thrombotic event to their death needs to be taken in the context of individual baseline characteristics that make a subgroup higher risk for thrombotic events.

And then lastly, so what can we do for thrombotic events that do occur? Well, certainly if a thrombotic event occurs, anticoagulation can be restored sooner because the risk-benefit analysis shifts to try to mitigate clot propagation in the setting of venous thromboembolism. IVC filters can be put in to prevent further VTE.

In addition, endovascular thrombectomy can be selected to extract clots that reach cerebral circulation and occludes large vessels, which has a number of needed to treat of about two for having a good outcome in patients with acute ischemic stroke.

So those are all the factors that are employed in that clinical setting. But again, I think the take-home point that shouldn't be overlooked is that all these thrombotic events need to be

considered in the context of an acute life-threatening bleed, where we've shown a substantial absolute risk reduction in not achieving hemostatic efficacy with treatment that translates to a number needed treat of seven to mitigate hematoma growth and establish hemostatic efficacy versus a thrombotic event rate of about 4.6 or excess thrombotic event rate with a number needed to harm of 22, which is threefold greater than a number needed to treat.

So in the totality of the data, there's a clear indication of overall benefit for these patients, and we just didn't have the power or appropriate length of follow-up to establish it within the trial.

Dr. Ahsan: Thank you. I think we're now going back to looping around to some additional questions. So Dr. Koroshetz, if you would like to ask your question, that would be great.

Dr. Koroshetz: Okay. So I'm going to go back to the question of your dose again. So certainly understand why you would want to completely get rid of the effects of the anticoagulants. But the question is, like we always try to be perfect, sometimes that's the enemy of good. And so I want to ask you about the procoagulant, potential procoagulant effects of andexanet alpha. So as it hasn't been mentioned here, but for weird reasons, I don't understand them all, but after an intracerebral hemorrhage, there's a really high risk of seeing ischemic strokes, small ischemic strokes around the brain. So we think that the intracerebral hemorrhage is putting the patient in a, actually an increased thrombotic state. Clear that these strokes are occurring in very commonly, maybe up to 30, 40% of people.

You see them on MRI scan. So we know we were in a hyper thrombotic state. Now there is a lot of literature out there, you know, that's been trying to follow the issue that we're concerned about here about thrombosis with the drug indicating that potentially the drug is doing more than blocking the anti-factor Xa drug.

So that includes increase in thrombin generation, increase in D-dimer, activation of the tissue factor, factor Xa complex to cause more factor Xa projection, which then gets more thrombin generation and so I guess I'd like the hematology folks to talk a little bit to the pro-coagulant effects of the high dose and whether or not that's actually something that needs to be addressed going forward.

And then I guess the other one is, you know, we talked about using heparin, but the drug blocks heparin effects. So, but I don't know what the time course of that is. So that's a secondary question.

Dr. Roe: Okay. For your first question, I'll ask Dr. Spyropoulos, to respond and describe the effects of andexanet in, what that means in reversing anticoagulation along all aspects and all parameters.

And then I believe your second question is about if heparin is started early as a re-anticoagulation strategy, is andexanet still around to potentially mitigate the impact of heparin? And I'll ask my colleague, Chris Penland, to respond to that question.

Dr. Koroshetz: Yeah, the drug blocks heparin.

Dr. Spyropoulos,: Yes, Alex Spyropoulos,. So I think these are a series of important questions. Again, to go back to your original discussion, our original discussion, thrombotic risk is mitigated by multiple factors, right? We all agree that the life-threatening bleed in and of itself produces a prothrombotic state, right? And patient-related factors, such as cardiovascular risk factors also put the patients at an increased risk of thrombosis. Now, in addition to sequestering and binding, again, the direct factor Xa inhibitors, I think there is data to show that andexanet also binds a tissue factor pathway inhibitor, which, as many of us know, is an endogenous anticoagulant targeting a tissue factor.

So there is data. If I can have that slide that shows the tissue factor TFPI and this hand in hand. So we do know that administration of andexanet is associated with a reduction in TFPI within about an hour of administration.

At the same time, what we can see on the right is that administration of andexanet within one hour also increases thrombin generation, as evidenced by the endogenous thrombin potential. And this is seen really in the first one to two hours after administration. Now, in my view, and the setting of a life-threatening bleed, this may be providential.

This may be an advantage because what it does is it enables a very rapid hemostasis in that timeframe. And then we see the effects over 12 hours with respect to thrombin generation are similar to those seen with the usual care arm, which, again, was mostly PCC. Now, whether the reduction of TFPI and also the increase in thrombin generation within that two-hour span, again, induces a potential prothrombotic state that's andexanet -related, I think remains to be seen.

So this is an important question. But again, what we see is the hemostatic effects, again, are very real and are associated with the first two hours of administration.

Dr. Koroshetz: What's the dose response to the thrombin generation?

Dr. Roe: So I'll ask my colleague Chris Penland to respond to that question.

Dr. Penland: The dose response to the thrombin generation is that both doses achieve approximately the same level of thrombin generation in the ANNEXA-I.

Dr. Ahsan: Great, thank you. Dr. Ratan.

Dr. Koroshetz: Sorry, the effect on heparin is gone? How fast is that going?

Dr. Roe: So yes, the duration of activity of andexanet, it declines. And so when heparin is used as a re-anticoagulation strategy, it is effective and it doesn't block that in that timeframe.

Dr. Koroshetz: How long is the effect for the Andexxa dose to block something like sub-q heparin, which is pretty low dose? How long would that effect last, the inhibition of the heparin after high dose, say, of andexanet?

Dr. Roe: Four hours of activity of andexanet.

Dr. Koroshetz : Thank you.

Dr. Ahsan: Great. We're pressing up against time, but I do want to get to Dr. Ratan and Dr. Wu. So Dr. Ratan, if you want to go ahead and ask a question.

Dr. Ratan: It seems an important driving assumption of andexanet is that decreasing hematoma size is going to be a major driver of neurological outcome and mortality. However, it seems like studies like MISTI, where they've been able to actually reduce the hematoma size and don't bear out the assumption that actually, unless you're reducing it at very low levels, that you're going to have a major effect on mortality. And that may relate to the fact that you still have red blood cells around that lyse and release things.

So I'm wondering whether there is additional data that the group has that suggests that reducing hematoma size for large to moderate hemorrhages, rather maybe than small hemorrhages, is really an important driver of the outcomes they're looking at.

Dr. Roe: To address the question on the impact of hematoma expansion on mortality rates downstream, I'll ask Dr. Shoamanesh to respond for us.

Dr. Shoamanesh: Well, I think it's, Ashkan Shoamanesh, I think it's undeniable there is a very rich and consistent body of literature that correlates hematoma expansion with poor outcomes. Particularly at timeframes beyond 30 days that were tested in ANNEXA-I, so at 90 days.

And now, actually, we've really learned that you need to get out to 180 or even 365 days to really see the benefit of acute treatments manifest themselves. And some of the data that led to that realization was actually the MISTI trial.

Now, what we know is that when you do an individual participant data analysis of all the literature, that the 35% threshold that was used with an ANNEXA-I, which is essentially very similar to the 33% that has been used in some of the ICH literature cutoff, has a 70% positive predictive value for an MRS of 4 to 6 at 90 days.

And just for visualization, MRS of 4 is moderate to severe disability, where someone needs another person for ambulation, severe disability being bedridden, and MRS of 6 being death. Now, it's also worth noting that the hematoma size, in relation to your question regarding how size interacts here, was actually 10 to 15 millimeters in the majority of ICH cohorts on factor Xa inhibitors. That's the median.

The median is about 20 cc. So the hematomas that were tested in these trials and the hematomas that we see on factor Xa inhibitors are not the very large hematomas that were evacuated in the MISTI study. Another variation, without taking too much time, is that the hematoma has already expanded in the MISTI trial.

Here, we're trying to mitigate the upfront expansion. So at one point, you're evacuating a hematoma that's already created a bunch of structural damage at its peak growth. That's the MISTI concept. Here, we're trying to minimize that structural damage from occurring in the first place.

Lastly, with the ENRICH study now, we actually have seen that in the right context with the right treatment, you can get benefits in mortality and functional outcome with evacuating hematomas. In the INTERACT-4 study, which was a study of acute blood pressure reduction pre-

hospital, in the ICH subgroup of that trial, where there was an absolute difference in a hematoma growth of 33 percent or greater of 7 percent, so half the effect size we saw for hemostatic efficacy, that translated in a larger trial in a reduction in death and disability on the MRS at 90 days.

So I think it's undeniable that hematoma growth drives poor outcomes in these patients and that reducing hematoma growth is clinically meaningful.

Dr. Ahsan: Great. Thank you. We can only take this last question from Dr. Wu, and then we'll have to move on. Dr. Wu, if you want to ask your question.

Dr. Wu: So I just want to get a clarification from the sponsor, whether they are checking the anti-factor Xa level before giving the drug, because you could have a patient who has a history of taking the apixaban, comes in with the bleed, but you don't know whether he or she's been taking it, when was the last dose.

And, you know, the same analogy is like, you know, you could have a patient history of taking Coumadin and comes in with the bleed, check the INR, the INR is completely normal. In that case, you wouldn't want to use vitamin K to reverse it. So in your case, are you checking the level anti-factor Xa before you give the drug or just give it to everybody who has a clinical history of apixaban use?

Dr. Roe: So I'll ask Per Ladenvall to respond to that question for the clinical trial, but in routine clinical practice, anti-factor Xa activity laboratory testing is not available widely for rapid testing like you could do for an INR current clinical practice. And Per will respond with respect to how that was done in the ANNEXA-I trial.

Dr. Ladenvall: So for, in the trial, there was only mandated anti-factor Xa levels if patients were presenting after 15 hours, or if there was an unknown time between last dose intake

and presentation. So for patients coming in earlier than 15 hours and where the time of treatment was taken, there was no mandated testing.

And of course, there is a balance between having availability of lab tests and delaying the treatment because the turnaround times for getting anti-factor Xa activity levels is even in those hospitals where that is available, delaying therapy with 30 minutes to 60 minutes. And worldwide, the availability of these tests at all, not around the clock, is somewhere around 20%. So we don't have the infrastructure to mandate lab testing in these acute settings.

Dr. Ahsan: Great. Thank you. If Dr. Ortel, I saw that you had raised your hand and lowered it quite quickly. If you had a quick question, we could probably manage, but if not, we'll conclude this session.

Dr. Ortel: Okay. I hope this is quick and easy to answer. I was just curious. We've been talking a little bit about the resumption of the anticoagulant in the post-treated bleed setting in order to try to mitigate or minimize as much as possible thrombotic events. And on, I think it's on slide 50, where you showed who received anticoagulants and who did not.

In the group that received anticoagulation, do you have available data on whether it was therapeutic versus prophylactic anticoagulation and timing, just to get some context of what seemed to be working here?

Dr. Roe: I'll ask Rohit Narayan to respond to that question.

Dr. Narayan: So with regards to the type of anticoagulation used in the study, over 70% of the patients actually did receive parenteral anticoagulation. But unfortunately, when we try to look further into the type of the dose, rather, of this anticoagulation, it's not really possible to determine whether these are therapeutic level dosings or whether they are, for example, VTE prophylactic dosings.

When we try to do a case-by-case assessment using medical judgment, it does appear that a lot of these parenteral anticoagulant dosings are indeed VTE prophylactic dosings. And here's a, you know, a Kaplan-Meier topograph of time to restart anticoagulation. We do see that for oral anticoagulation restart, that happens very, very late in the study, actually, compared to the overall time of restarts of anticoagulation.

So if I show here this for oral anticoagulation, only about 10% of patients are receiving an oral restart of anticoagulation in the study, which kind of reflects what has been suggested before, that restarting therapeutic anticoagulation usually occurs much, much later due to this individualized risk assessment.

Dr. Ahsan: Great. Thank you very much. I'd like to thank Dr. Roe for moderating this session and all the applicant speakers for providing thoughtful answers to the questions from the committee. At this point, we're going to move on to the FDA presentations. Let's see. And Dr. Knoll will be presenting. We'll also have an opportunity for Q&A at the back end of that presentation. Okay, thank you.

FDA Presentation – sBLA 125586/456: Christine Knoll, M.D.

Dr. Knoll: Good morning, and thank you to the members of the committee, the AstraZeneca team, patients, invited guests, and FDA colleagues. I'm Christine Knoll, and I'm a Pediatric Hematologist and clinical reviewer in the Office of Clinical Evaluation. I will present the efficacy portion of the application, and my colleague, Dr. Karl Kasamon, will present the safety review.

Members of the review team are presented here, and the FDA presentation reflects the collective input. During our presentation, we will describe the purpose of this meeting, provide an overview of bleeding associated with direct oral anticoagulants, describe andexanet and its

regulatory history, and review the ANNEXA-I trial and results. We will conclude by presenting the topics for which we are seeking the committee's thoughtful discussion and recommendations.

We referred this supplemental BLA to the advisory committee to discuss whether the applicant has provided evidence to verify the clinical benefit of andexanet for the indication approved under the accelerated approval pathway. ANNEXA-I is a randomized, controlled trial of andexanet compared to usual care conducted to verify clinical benefit. andexanet met the primary efficacy endpoint of effective hemostasis at 12 hours. However, the treatment effect on other endpoints evaluated in ANNEXA-I that may provide a measure of long-term benefit appeared comparable across both arms.

We are also seeking the committee's discussion on the benefit and risk assessment of andexanet in the context of the increased incidence of thrombosis observed in the andexanet arm compared to the usual care arm.

Next, I will provide an overview of the incidence of life-threatening bleeding due to the use of direct oral anticoagulants. Direct oral anticoagulants, or DOACs, are the predominant class of oral anticoagulant agents used for the treatment and prevention of thrombosis. Two to four percent of patients taking direct oral anticoagulants have major bleeding events per year, and this bleeding can carry high morbidity and mortality. Bleeding may be severe and may require reversal of the anticoagulant.

Andexanet was approved for the reversal of two direct oral anticoagulants, apixaban and rivaroxaban, in patients with life-threatening or uncontrolled bleeding. Prior to the accelerated approval of andexanet, prothrombin complex concentrates were the predominant reversal products used to treat life-threatening bleeding associated with anticoagulation.

While prothrombin complex concentrates may be effective, they are not a direct reversal agent or antidote for direct oral anticoagulants.

I will now provide a brief description of andexanet's mechanism of action. I will also briefly describe the regulatory history for andexanet, focusing on key interactions with the agency that are relevant to today's meeting. Andexanet is a recombinant variant factor Xa that binds to direct oral anticoagulants but has been modified so that it cannot catalyze the coagulation reaction. It has two procoagulant mechanisms of action. The first is to sequester direct oral anticoagulants, leading to a decrease in anti-Xa lasting approximately two hours.

The second procoagulant mechanism of action is to inhibit tissue factor pathway inhibitor, or TFPI, leading to an increase in tissue factor-activated thrombin generation, and this effect lasts approximately 96 hours.

While both mechanisms contribute to therapeutic and pathologic effects, including thrombosis, the relative contribution of each mechanism is unclear. Before discussing the andexanet regulatory history, I will remind the committee and the public of FDA's evidentiary standard for approval because we are asking the committee to provide input on the data package which AstraZeneca submitted to verify clinical benefit. To receive approval, an applicant must provide evidence that the drug is safe and effective for its intended use.

The data must come from adequate and well-controlled trials. There are two approval pathways. Traditional approval is generally granted to drugs that demonstrate clinical benefit as measured by effects on how a patient feels, functions, or survives.

Accelerated approval is granted to drugs that treat serious conditions and have meaningful advantage over available therapy. The endpoint measure must be reasonably likely to

predict clinical benefit. In granting accelerated approval, FDA may require confirmatory trials to verify and describe clinical benefit.

With this background, andexanet was granted accelerated approval in 2018 for patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. This was based on a proposed surrogate endpoint of a change from baseline in anti-Xa activity in healthy volunteers. At the time of approval, a post-marketing randomized controlled study was required to verify clinical benefit.

The applicant proposed ANNEXA-I as the confirmatory trial to fulfill the accelerated approval post-marketing requirement. At the time of the initial protocol submission, the primary efficacy endpoint was a composite of two components, change in hematoma volume and NIH stroke scale, which I will describe in later slides. The applicant then submitted a protocol amendment, which included changes in the primary efficacy endpoint. The sponsor added a third component to the composite endpoint to include the need for rescue intervention.

The FDA provided feedback on the composite endpoint, which now included the following, change in hematoma volume, NIH stroke scale, and the need for rescue intervention at 12 hours as a measure of effective hemostasis. FDA recommended that longer-term outcome measures of neurologic function, such as Glasgow outcome score or the modified Rankin score, assessed at 90 days would better account for treatment effects on hemostasis and perihematoma edema. However, the FDA recommended changes to the primary efficacy endpoint were not implemented in the protocol.

In January 2024, the supplemental BLA package was submitted to support conversion of andexanet's accelerated approval to traditional approval. I will now turn to the review of the efficacy portion of the supplemental BLA, starting with the ANNEXA-I trial design.

ANNEXA-I is a Phase IV open-label, randomized, multi-center trial of andexanet in patients on direct oral anticoagulants presenting with intracranial hemorrhage to evaluate its safety and efficacy compared to usual care. Patients were eligible to enroll if they presented within six hours of acute intracranial hemorrhage symptom onset and no more than 15 hours after receiving the last dose of their direct oral anticoagulant. Patients were randomized one-to-one to receive andexanet or usual care.

Patients randomized to the andexanet arm received andexanet at the approved dosage that I will describe in a subsequent slide. Patients randomized to the usual care arm received treatment at the discretion of the treating physician. This consisted of any treatment, including no treatment other than andexanet, that the investigator considered to be appropriate.

The primary efficacy endpoint was hemostasis at 12 hours, and the primary safety endpoint was the occurrence of thrombotic events. The study duration was 30 days. Shown in this slide is a more detailed description of key criteria for entry into ANNEXA-I. The study enrolled patients with intracranial hemorrhage with hematoma volumes between 0.5 and 60 milliliters.

Baseline imaging confirming bleeding had to be obtained within six hours of symptom onset. The last dose of the direct oral anticoagulant had to be less than 15 hours prior to randomization. However, if the last dose was more than 15 hours prior to randomization or the timing of the last dose was unknown, patients could be eligible if the local anti-Xa activity level was greater than 100.

Patients were also required to have an NIH stroke scale score of 35 or less, a glass glaucoma scale score of 7 or higher, and to have no thrombotic event within the last two weeks prior to study entry.

This figure depicts the schedule of assessments from pre-randomization through 12 hours post-randomization. andexanet was to be initiated no later than 30 minutes after randomization and within two hours from baseline imaging.

Usual care was to be initiated within three hours post-randomization. As noted in an earlier slide, andexanet was administered to patients randomized to the investigation alarm according to approved dosage. andexanet is approved for IV administration at a low and high dose.

Andexanet is administered as an initial bolus followed by a two-hour infusion in both low and high dose. Dosing is dependent on the specific direct oral anticoagulant that andexanet is intended to reverse, either rivaroxaban or apixaban, and is based on the timing and last dose received as shown on this slide.

The primary efficacy endpoint was effective hemostasis at 12 hours post-randomization based on the following three components. Brain imaging to assess hematoma expansion, NIH stroke scale to evaluate acute to clinical outcome, and the need for rescue intervention. I will discuss these components in more detail in the next slide.

As shown on this slide, the determination that effective hemostasis was achieved was based on the requirement that all of the following criteria were met. With regards to brain imaging to assess hematoma expansion, a change in hematoma volume at 12 hours post-randomization of 35% or less was considered achievement of hemostasis.

An outcome categorized as good was one where the change in hematoma volume was between 21% and less than or equal to 35%. An outcome categorized as excellent was one where the change in hematoma volume was less than or equal to 20%.

With regards to the second component, NIH stroke scale, a score of less than plus seven point change from the baseline score at 12 hours post-randomization was considered good or excellent.

The final component of the composite primary efficacy endpoint to be considered good or excellent outcome was that the patients could not have received rescue intervention between 3 and 12 hours post-randomization. Rescue intervention was defined as any treatment specifically intended to address continued or recurrent bleeding, and this included administration of blood products except packed red blood cells or platelets, administration of pro-coagulant factor infusions, or systemic hemostatic therapy except tranexamic acid, and any unplanned rescue surgical procedure intended to treat the hematoma.

Listed on this slide are the secondary and select additional efficacy endpoints. The secondary efficacy endpoint was percent change from baseline to the lowest level in antigen activity during the first two hours post-randomization. Additional select efficacy endpoints focused on neurologic outcomes at later time points, including neurologic deterioration at 24 hours and modifying Rankin scale score at 30 days.

Neurologic deterioration at 24 hours was defined as an NIH stroke scale score increased greater than or equal to 4 or a Glasgow Coma scale score decrease greater than or equal to 2 compared to baseline. The NIH stroke scale score measures stroke severity with higher scores indicating more severe neurologic deficit. The Glasgow Coma scale is used to objectively describe the extent of impaired consciousness in acute medical and trauma patients with lower scores indicating lower levels of consciousness, and the modified Rankin scale or MRS measures neurologic functional independence for higher scores to the worst neurologic function with the highest score of six being death.

I will now briefly describe the statistical analysis plan, which the applicant discussed in their presentation. ANNEXA-I applied a group sequential design with two looks, one interim and one final. The interim analysis was planned after about 50% of the patients had been adjudicated for hemostatic efficacy.

A type alpha spending function was planned to control the overall type one error. The allocated alphas were 0.0310 at interim and 0.0277 at final analysis. The primary efficacy analysis was based on the intention to treat analysis set using the Cochrane-Mantel-Hansel method, stratified by time from symptom onset to the baseline imaging scan of less than 180 minutes versus greater than or equal to 180 minutes. And patients with non-evaluable effective hemostasis status were classified as having poor efficacy outcome.

As presented in the previous slide and in the applicant's presentation, an interim analysis for efficacy was performed when 50% of the planned study population was adjudicated for hemostatic efficacy. As a result, 452 patients were included in the interim analysis and constituted the primary efficacy population.

The FDA analysis excluded a subgroup of patients who were taking edoxaban and enoxaparin because these anticoagulants are not relevant to the indication in the label. The FDA primary efficacy analysis was based on this subset of the primary efficacy population. A total of 404 patients had been randomized who had received apixaban or rivaroxaban, with 204 in the andexanet arm and 200 in the usual care arm.

The extended population consisted of the primary efficacy population, plus those patients enrolled on the study after the interim analysis data cutoff date through the stopping of the trial. The extended population was used for the safety analyses and for sensitivity analyses for

efficacy. This population included 474 patients total with 241 in the andexanet arm and 233 in the usual care arm.

The efficacy population for andexanet that included apixaban and rivaroxaban treated patients consisted of 404 patients. 31% of patients had protocol deviations, missing and or discrepant data that impacted the efficacy assessment. These patients were balanced across treatment arms and the FDA compared analyses, including and excluding the subset of patients, and the results were similar.

I will now present the study efficacy results. The efficacy population demographics and baseline characteristics are shown on this slide. You will note that the demographics and baseline characteristics appear generally similar across both arms. The only exception was that there was a higher number of patients who received apixaban for anticoagulation pre-study compared to rivaroxaban. Of note, most patients in both arms were receiving anticoagulation due to a history of atrial fibrillation. The average time to treatment administration was comparable across both arms with 25 minutes for the andexanet arm and 30 minutes for the usual care arm.

Based on the previously mentioned dosing algorithm, most patients received low dose andexanet at 79%. This figure represents the disposition of patients in ANNEXAI. A total of 404 patients were randomized at the time of the interim analysis data cutoff date.
204 patients were randomized in the andexanet arm with 145 patients completing the study and 59 patients discontinuing. 200 patients were randomized in the usual care arm with 147 patients completing the study and 53 patients discontinuing. Death was the most common reason for study discontinuation in both arms.

The primary efficacy endpoint of effective hemostasis at 12 hours was met with 66% of the andexanet arm having excellent or good outcome versus 53% of the usual care arm. This 12% difference was statistically significant with a p-value of 0.0113.

As shown on this slide, the largest treatment effect was in one of the three components of the composite endpoint. This is highlighted by the red box which shows hematoma volume change of less than or equal to 35% in 74% of patients in the andexanet arm versus 60% in the usual care arm.

Andexanet appears to have smaller positive effects on the other two components of NIH Stroke Scale and the use of rescue therapy. For the secondary efficacy endpoint of percent change from baseline to nadir and anti XA activity during the first two hours post-randomization, treatment with andexanet resulted in a median reduction of 95% in anti-Xa compared to 29% in usual care. This slide shows the anti-Xa levels by response status in both arms as measured by successful hemostasis.

The red box highlights that in andexanet treated patients, the percent change from baseline to nadir and anti-Xa levels was comparable between responders and non-responders. A similar trend is observed in the usual care arm.

Now moving on to additional select efficacy endpoints. This slide shows results of neurologic outcomes including neurologic deterioration at 24 hours, modified rank and scale scores at 30 days compared to baseline, and mortality in both treatment arms. As shown in the first row of the table, neurologic deterioration at 24 hours was similar between both arms with 32% in the andexanet arm and 29% in the usual care arm.

I now want to focus your attention to the second row and as a reminder the modified rank and scale score is a measure of neurologic functional independence and an MRS of 0 to 3 is considered functionally independent, meaning these patients are able to walk without assistance.

An MRS of 4 to 6 is considered functionally dependent, ranging from walking with assistance to death as the score of 6. Back to the second row, among patients who had a baseline MRS of 0 to 3, a slightly smaller proportion of patients in the andexanet arm had stable MRS scores at day 30 compared to patients in the usual care arm at 32% versus 39%. Also among patients who had a baseline MRS of 0 to 3, a slightly greater proportion of patients in the andexanet arm had a worsening of their MRS at day 30 compared to usual care arm at 68% versus 61%.

Now if you look at the third row, among patients who had a baseline score of 4 to 6, the proportion of patients with stable MRS at day 30 is comparable in both arms with 88% in the andexanet arm versus 92% in the usual care arm. Also among patients who had a baseline score of 4 to 6, the proportion of patients with an improvement in MRS was also comparable at day 30 with 12% in the andexanet arm and 8% in the usual care arm.

Finally, the last row shows that mortality was similar in the andexanet and care arms at 26% in each. This slide shows results of neurologic outcomes in responders in both treatment arms. And as a reminder, a responder here denotes good or excellent hemostatic outcome at 12 hours. As shown in the first row of the table, a larger proportion of responders in the andexanet arm had neurologic deterioration at 24 hours compared to responders in the usual care arm at 16% versus 5%.

I now want to focus your attention again to the second row. Among responders who had a baseline MRS of 0 to 3, a smaller proportion of patients in the andexanet arm had stable scores at

day 30 compared to responders in the usual care arm at 41% versus 59%. Also, among responders who had a baseline score of 0 to 3, a larger proportion of responders in the andexanet arm had a worsening of the MRS score at day 30 compared to the usual care arm at 59% versus 41%. Now, if you look at the third row, among responders whose baseline MRS was 4 to 6, the proportion of responders with stable MRS at day 30 is comparable in both arms with 83% in the andexanet arm versus 87% in the usual care arm.

Also, among patients who had a baseline MRS of 4 to 6, the proportion of patients with an improvement in MRS was also comparable at day 30 with 17% in the andexanet arm and 13% in the usual care arm. Finally, the last row shows that mortality was higher in responders in the andexanet arm compared to the usual care arm at 16% versus 9%.

To summarize, more patients in the andexanet arm with a modified Rankin score of 0 to 3 at baseline had a change to a score of 4 to 6 at day 30, meaning more patients in the andexanet arm who were able to walk without assistance at baseline were not able to walk or had died by day 30. And this was also seen amongst responders in the andexanet arm.

To summarize, the efficacy data provided in the supplemental BLA shows that ANNEXA-I met efficacy criterion for success at interim analysis with a study demonstrating that patients randomized to treatment with andexanet met the primary endpoint of hemostatic efficacy with 66% in the andexanet arm and 53% in the usual care arm, achieving successful outcome of good or excellent. While the superiority of the primary efficacy endpoint of hemostatic efficacy was met, the largest treatment effect was in change in hematoma volume at 12 hours, with smaller positive effects on the other two components of the primary efficacy outcome of NIH stroke scale and use of rescue therapy.

The secondary efficacy endpoint of percent change from baseline to data in anti-Xa activity during the first two hours post-randomization showed that treatment with andexanet resulted in a median reduction of 95% in anti-Xa compared to 29% in usual care. However, this anti-Xa reduction did not correlate with hemostatic efficacy as the change from baseline to data in anti-Xa levels was comparable between responders and non-responders as measured by successful hemostasis.

Finally, additional efficacy endpoints of longer-term clinical outcomes showed the following. Neurologic deterioration at 24 hours and mortality were comparable between andexanet and usual care arms. However, there were more responders with neurologic deterioration at 24 hours and higher mortality in the andexanet arm compared to usual care. Analysis of MRS, or modified Rankin scale, showed that a smaller proportion of patients in the andexanet arm maintained a baseline of 0 to 3, with a larger proportion experiencing worsening of MRS at 30 days compared to baseline in the andexanet arm.

Therefore, more patients in the andexanet arm who were able to walk independently at baseline were not able to walk independently or had died by day 30. This was also seen among responders in the andexanet arm. Therefore, successful outcome of the primary endpoint at 12 hours did not translate to successful longer-term clinically meaningful outcomes.

I will now turn over the presentation to my colleague, Dr. Karl Kasamon.

FDA Presentation – sBLA 125586/546: Karl Kasamon, M.D.

Dr. Kasamon: Thank you, Dr. Noll. My name is Karl Kasamon. I'm a hematologist and a member of the review team. And I will describe the safety portion of this application, summarize the clinical data, and then close with the topics for discussion.

The safety analyses in ANNEXA-I were descriptive and were conducted based on the actual treatment that the patients received.

Select safety endpoints in ANNEXA-I included incidents of adverse events, thrombotic events, mortality, and hospitalization outcomes. The FDA safety analysis population consisted of all patients treated in ANNEXA-I through the study end date, excluding patients who had been treated with edoxaban and enoxaparin.

The median age of patients enrolled in ANNEXA-I was 80, and most were white. As shown in this slide, the study arms were balanced with respect to demographic characteristics. Adverse events were balanced between the two arms, and the types of adverse events reported were those that may be expected in patients who are hospitalized for hemorrhagic stroke and who may be non-ambulatory for a period of time. And these include infections such as urinary tract infections and pneumonia.

As you can see on this slide, there were numerically more ischemic strokes in patients who received andexanet compared to those who received usual care. There were more post-treatment intracranial hemorrhage events among patients who received usual care compared to those who received andexanet. Given that the presence of intracranial hemorrhage was a study entry criterion, to be considered an adverse event, the intracranial hemorrhage event had to be a new occurrence or a hematoma expansion past the primary efficacy endpoint of 12 hours.

As you had seen in the applicant's presentation, the proportion of patients with serious adverse events, or SAEs, was numerically higher in the andexanet arm, 46%, compared to the usual care arm at 37%. This table highlights the neurologic serious adverse events. The most common neurologic serious adverse events were ischemic stroke and cerebral hemorrhage for

patients who received andexanet, whereas intracranial hemorrhage was the most common neurologic serious adverse event in usual care patients.

Listed here are the non-neurologic serious adverse events. And the most common non-neurologic serious adverse events among andexanet-treated patients included myocardial infarctions and infections such as pneumonia. Among usual care-treated patients, the most common events included infections, especially pneumonia.

Listed in this slide are adverse events that led to death. The most common adverse event leading to death in both andexanet and usual care patients was intracranial hemorrhage, followed by infections and ischemic stroke. Patients on both arms had comparable lengths of days hospitalized, duration of stay in the intensive care unit, and hospital readmissions within the first 30 days.

Thrombotic events are a major safety concern for this application. Adverse events that constitute thrombotic events were adjudicated by the FDA review team on the basis of case report forms, narrative histories, and requests for information during review of the application. As shown in this slide, 14.6% of patients who received andexanet experienced a thrombotic event compared to 6.9% of those who were treated with usual care, translating to a difference in the rate of these events of nearly 8%.

As shown in this slide, you'll see a more detailed presentation of thrombotic events occurring in ANNEXA-I. A total of 35 andexanet-treated patients experienced 42 thrombotic events, while 16 patients treated with usual care experienced 18 thrombotic events. Among andexanet-treated patients, the most prevalent thrombotic events were arterial, such as ischemic strokes and myocardial infarctions. In the usual care-treated patients, pulmonary emboli were the most common thrombotic events.

The results of our analysis to assess the timing of thrombotic events in ANNEXA-I are shown in this slide. The first row represents the patients who developed thrombotic events. In andexanet-treated patients, thrombotic events occurred at a median of 3.5 days following treatment, compared with a median of 16 days among usual care-treated patients, as shown in the second row.

In the third row in this table, you'll see that a total of 17 out of the 35, or 49%, of andexanet-treated patients experienced TEs, and they did so by day 3. This compares with only 1 out of 16 patients, or 6%, of usual care-treated patients. I will point out that anticoagulation as a prophylactic measure was defined as treatment with one or more doses of an anticoagulant during the follow-up period after study treatment administration and before occurrence of the first TE. In red, at the bottom, you will notice that in both arms, approximately half of the patients with TEs had experienced the first TE following the initiation of prophylactic anticoagulation.

This slide illustrates anticoagulant use in ANNEXA-I after study treatment completion. Andexanet-treated patients are shown in blue, and usual care-treated patients are in gray. The x-axis shows the study day. The red circles indicate thrombotic events, whereas black squares indicate patient death. The thin green lines indicate duration of anticoagulant. Among the Andexanet-treated patients, you will notice that TEs tended to occur earlier, and just over half of the TEs occurred prior to the start of prophylactic anticoagulation.

You can also see that TEs also occurred while patients had been started on prophylactic anticoagulation. Among usual care-treated patients, the TEs occurred somewhat later compared to andexanet-treated patients, and the TEs also occurred in some patients treated with prophylactic anticoagulation. Among the 165 andexanet-treated patients and 163 usual care

patients who resumed anticoagulation as a prophylactic measure, 10% of andexanet-treated patients developed a TE, compared with 6% of usual care-treated patients who resumed anticoagulation prophylactically.

In this last row, you will notice that among the 74 andexanet-treated patients and 69 usual care patients who did not resume prophylactic anticoagulation, thrombotic events occurred at a rate of 26% in andexanet-treated patients compared with 10% of usual care. With respect to the review of deaths in ANNEXA-I, the death rate within 30 days of randomization appears similar between andexanet- and usual care-treated patients at 28% versus 26%, respectively. Six of the deaths in andexanet-treated patients were attributable to TEs compared with two deaths in usual care-treated patients.

To summarize the key findings of the safety review, please note the following. The rate of TEs after andexanet treatment was 14.6% compared to 6.9% with usual care. TEs tended to occur earlier in andexanet-treated patients compared to usual care-treated patients, and nearly half of the patients with a TE developed it on prophylactic anticoagulation. Deaths due to TEs were higher in andexanet-treated patients compared to usual care patients.

I would like to now summarize the FDA presentation. The study met the primary efficacy endpoint of effective hemostasis at 12 hours. This primary endpoint was a composite consisting of hematoma volume change, NIH stroke scale, and the use of rescue therapy. The largest treatment effect was in the change in hematoma volume at 12 hours. While guidelines recommend imaging at later time points, such as at 24 hours, these data were not submitted for review within the SBLA submission. An information request had been sent with an incomplete response received. Andexanet had smaller positive effects on the other two components of the primary efficacy endpoint, specifically NIH stroke scale and the use of rescue therapy.

The secondary efficacy endpoint of percent change in anti-TE activity was also met. The decrease from baseline in anti-TE activity was greater in andexanet than in usual care, with 95% reduction in andexanet arm compared to 29% in usual care. However, there was no correlation between anti-Xa activity reduction and hemostasis. Thus, an ANDEXXA-I confirmatory study demonstrated that the decrease in anti-Xa did not predict clinical benefit, which had been the basis of the accelerated approval.

Finally, additional efficacy endpoints of longer-term outcomes showed that neurologic deterioration at 24 hours and mortality were comparable between the two arms. Analysis of MRS score showed that slightly more patients in the usual care arm maintained their baseline MRS score at day 30 compared to the andexanet arm. There were also slightly more patients in andexanet arm with a change from their baseline MRS score to 30 days, including a worsening of the score, meaning that patients in andexanet arm who were able to walk without assistance at baseline were unable to walk or had died by day 30.

If we focus only on patients who were responders by the primary efficacy endpoint, neurologic deterioration and mortality were higher in andexanet responders compared to usual care responders. When evaluating MRS, more andexanet responders demonstrated a worsening outcome at 30 days compared to baseline, while more usual care responders maintained a stable MRS at 30 days. This demonstrates that a successful outcome of the primary endpoint at 12 hours did not translate to successful longer-term outcomes.

These longer-term outcome measures are clinically meaningful and should be considered in assessing the magnitude of the clinical benefit.

The rate of thrombotic events was double in andexanet-treated patients compared with the usual care. TEs occurred much earlier in Andexanet-treated patients with a median of 3.5

days to the first TE versus a median of 16 days in usual care. During this very early period after a life-threatening bleed, there may be delays in resuming of anticoagulation. Nearly half of the TEs occurred in patients who had already resumed prophylactic anticoagulation. The earlier onset of TEs in the andexanet arm compared to usual care raises questions regarding the effectiveness of prophylactic anticoagulation to mitigate the risk of thrombosis in patients with recent symptomatic intracranial hemorrhage.

Finally, deaths from TEs were higher in andexanet arm compared with usual care. Overall, the safety concern of TEs appears challenging to medicate. The results of ANNEXAI, a trial intended to verify and describe the clinical benefit of Andexanet in the approved indication, do not show a correlation between the change in anti-Xa activity from baseline to , this endpoint which had been used to support the initial accelerated approval, and effective hemostasis, this study's primary efficacy endpoint.

ANDEXXA-I demonstrated a statistically significant improvement in achieving hemostasis at 12 hours with 66% of patients randomized to andexanet meeting this endpoint compared with 53% of patients randomized to usual care. But as noted, the treatment effect was most pronounced in the component of the composite endpoint that measures change in the volume of bleed. In a patient population with symptomatic intracranial hemorrhage, the clinical meaningfulness of this outcome is unclear in the absence of data demonstrating longer-term hematoma volume control beyond 12 hours and longer-term neurologic outcomes that were proposed by the FDA.

Andexanet has a serious risk of thrombosis. The rate of thrombotic events in andexanet-treated patients was double that of those who received usual care. Thrombotic events among andexanet-treated patients tended to occur earlier than in usual care-treated patients and

continued to occur while on prophylactic anticoagulation. And deaths attributable to TEs were double the rate in the andexanet arm compared to usual care. It is therefore unclear whether the treatment with andexanet provides a clinically meaningful benefit to patients, especially in the context of these serious risks.

Next, I will move on to the discussion topics. At this time, we would like to ask the committee members to discuss and provide comment on the topics presented here. First, the primary efficacy endpoint of ANNEXA-I was met, with the largest treatment effect from among the three endpoint components being the change in the hematoma volume at 12 hours. However, other clinically meaningful outcomes, for example, neurologic status at 24 hours and overall mortality, were not different between the two arms. And MRS at day 30 was worse in andexanet arm.

Please discuss whether the treatment effect on the study's primary efficacy endpoint constitutes a clinical benefit to patients. Specifically, please provide comment on whether an effect on hematoma volume change at 12 hours alone constitutes a clinical benefit.

Please provide your comments on neurologic status at 24 hours, MRS at day 30, and overall mortality, and whether these outcomes should be incorporated into the assessment of clinical benefit.

Additionally, please comment on the reduction from baseline in anti-Xa activity and its role in assessment of the benefit of Andexanet. And in terms of safety, the ANNEXA-I demonstrated an increased incidence of thrombosis, 14.6% versus 6.9%, and thrombosis-related deaths at day 30, 2.5% versus 0.9% in Andexanet-treated patients versus usual care.

We ask the committee to comment if the serious risks of andexanet, as demonstrated in ANNEXA-I, are acceptable in the indicated population and in the context of the clinical efficacy demonstrated in ANNEXA-I. Thank you.

FDA Presentation – sBLA 125586/546: Q & A

Dr. Ahsan: Great. Thank you, Drs. Knoll and Kasamon for that presentation to help gear us. I'm going to ask one quick question, taking chair discretion here. Dr. Kasamon, could you tell me or elaborate a little bit more this MRS baseline value? It did seem that when the patients had a baseline value between 0 and 3, that treatment with this product led to a decrease in neurological or an increase in neurological deterioration. But when their MRS values were at baseline of 4 to 6, there didn't seem to be much change between the usual care group and the experimental group.

So could you tell me also about the mortality? Do you have data on stratifying the mortality based on MRS baseline values?

Dr. Kasamon: I'm afraid I don't have the data. I would like to ask Dr. Knoll, but I'm not sure.

Dr. Knoll: No, We do not have that data. Good question.

Dr. Ahsan: Does that seem like reasonable information to look at? You know, the applicant talked about how the thrombosis events, the TEs were stratified as respect to medical history for ischemic stroke and MI. So I was wondering if whether the MRS baseline leads to some mortality. Maybe if the applicant has a quick answer to that question, does the sponsor want to answer, Dr. Roe?

Dr. Roe: A question about how baseline MRS results correlated with downstream mortality. We'd like to come back after the break with a full, complete response to that question.

Dr. Ahsan: That would be helpful. Thank you. Okay. Dr. Koroshetz, would you like to ask your question?

Dr. Koroshetz: A whole bunch of questions, but the first one was I had thought, and maybe I'm mistaken, that there were more events in the high-dose group than the low-dose. Is that correct?

Dr. Kasamon: Yes, that is correct.

Dr. Koroshetz: I assume thrombotic events, yes.

Dr. Kasamon: We actually have a backup slide that just has that information.

Dr. Koroshetz: And then the, so in terms of the timing, you show the dots and the x-axis is days, but I'm guessing that, you know, it's between zero and one day is a dot at one day and zero and two days is a dot at two days. Is that, it's not an actual clot time or is it? Dr. Kasamon: So, it is clot time.

Dr. Koroshetz: It is clot time.

Dr. Kasamon: The dots are study days or the –

Dr. Koroshetz: Study days, but not hours. So, it's rounded out to days. Is that what it is?

Dr. Kasamon: That's correct. Yes.

Dr. Koroshetz: Got it. Okay. All right. Thank you.

Dr. Ahsan: Okay. Dr. Ratan, would you like to ask your question?

Dr. Ratan: Yeah. I don't know if this, if you can answer this question, but did, is there, was there a reason given, let me do my, for some reason the video is not going on, but the, is there a reason why it's fairly standard to look at MRS at 90 days because MRS at 30 days is still highly variable.

And so, I'm curious whether there was some discussion of why they looked at, and for many stroke studies, they do 90 days or further because, especially when it comes to disability,

it's a, it is a highly dynamic time. So, is there any explanation of why that would be a reasonable time to look?

Dr. Kasamon: I, I think I, I agree with that sentiment, but I would probably invite the applicant to, to perhaps address that.

Dr. Roe: Suitability of MRS at 30 days versus a 90-day follow-up. I'll ask Dr. Shoamanesh to respond.

Dr. Shoamanesh: So, I agree with the comment, Ashkan Shoamanesh, I'm sorry. I agree with the comment that 30 days is not a suitable timeframe to look at the MRS. But as you heard from the sponsor earlier, by the time that a recommendation had been made to consider longer-term endpoints on the, for the MRS in particular, many patients in the trial had already surpassed 90-day follow-up.

And it would have been impossible to go back and get it in any reliable way retrospectively. And our average enrollment rate in the study was one patient per center per year, just to put in the context. And thus, the 30-day window was really the predefined window for safety outcomes. And an MRS was captured just to have some data on it. But as you've alluded to, the standard thus far has been 90 days for stroke trials. That's been adopted from the plateau seen in ischemic stroke patients.

And in reality, now we know for ICH patients, we even need to go beyond 90 days to 180 to 365 days to really see the full effect of acute interventions. And thus, in my view, on the basis of all that, and actually your concern, which I share, I do not believe the 30-day MRS is informative in any way regarding the effects of andexanet on functional outcome.

Dr. Ratan: Can I have a follow-up to that, Dr. Shoamanesh?

Dr. Ahsan: Go ahead..

Dr. Ratan: So one question is, I mean, others, as you know, have, instead of looking at the bending it into zero to three and four to six, which is a little bit arbitrary, Kennedy, Lees, and others have looked at how people have shifted from one MRS number to another. Did you ever try to do an analysis where you looked at, you know, what percentage of patients went from, you know, shifted by one or two levels? I think it's been – I don't remember specifically how they've done it in the past, but rather than simply bending into two arbitrary groups, because from a disability standpoint, there are no scales. And I think it kind of gets to Tabby's initial question, you know, about what's the meaning of looking at these, bending it in this way.

Dr. Roe: We will come back after the break to address your question on changes in MRS broken down into ordinal scale, like you described.

Dr. Ahsan: Yeah, that would be helpful because the way it's been, you know, with just one patient this way or that way was making a change in the percentage that looked more interesting than maybe it really was.

Okay. Thank you, Dr. Ratan, for that question. Dr. Kindzelski.

Dr. Kindzelski: Yes, thank you. I want to follow up on the question that Dr. Koroshetz asked about the graphical representation of the timeline of thrombotic event and start of the anticoagulation in those patients. Considering that those are days, is it possible that thrombotic event led to initiation of anticoagulation? Because in many dots and green lines, they kind of coexist. Is it possible to have a more detailed timeline for I think it is important.

Dr. Kasamon: So perhaps we could show slide 48 of the presentation, which has that illustration. And so in this slide, you know, we have highlighted that the definition of prophylactic anticoagulation was simply when the anticoagulant had been started prior to the diagnosis of any TE in a given patient after, say, andexanet administration.

And so you will notice that any red dots on the left, to the left of the start of the green line represent thrombosis, that thrombotic events that occurred before and without any prophylactic anticoagulation. And then conversely, where a green line starts without any red dot to the left of it, and then there is a red dot, it indicates that that patient had been started on prophylactic anticoagulation, and then the thrombosis occurred.

Dr. Kindzelski : Right. But what about line one, line four, line eight, line 19, 20? Does that mean that anticoagulation started immediately after thrombotic event?

Dr. Kasamon: No. So I believe three out of the four andexanet ones were technically prophylactic by that definition, meaning that they were started on the same day, but prior to the description of the TE. Hematologically, that means that there was clearly not enough time for the anticoagulant to have really prevented that thrombosis, but that was the approach. And then the remainder were actually treatment initiations of anticoagulation due to the thrombosis. That is a good question. Thank you.

Dr. Kindzelski Thank you.

Dr. Ahsan: Yeah. I mean, I think that that's the question is the sequence of events, right? Whether the TE resulted in the anticoagulation treatment being started. It looks like the sponsor might have a comment, a quick comment on that. As long as it's data-driven, that would be acceptable.

Dr. Roe: Yeah. Yes. The comment and the response is it was not randomized as to when and how anticoagulation was started. It was up to the physician's discretion. I'll ask my colleague, Rohit Narayan to provide further details on the timing and sequence of restarting of anticoagulation and the occurrence of thrombotic events.

Dr. Narayan: So with regards to your question about did patients who have a thrombotic event, did they initiate anticoagulation afterwards? And I think it's very important to differentiate between a prophylactic dose of anticoagulation and therapeutic dosing of anticoagulation. And within the first seven days of the study, no patient actually received any oral anticoagulation, even if they developed a thrombotic event.

Now, when we do look into the dosings of anticoagulation, I had mentioned before that this was not specifically recorded with regards to parenteral on what level of anticoagulation was provided, whether it was therapeutic or whether it was treatment dose.

When we do look into cases on a medical case-by-case basis, looking at the specific doses, if it was provided, being used, the majority of parenteral anticoagulation initiated was at typical VTE prophylactic dosings. And even if patients did have arterial events, for example, few of them were actually initiated looking on this kind of medical case-by-case basis with a therapeutic dose anticoagulation. It tended to be that these patients were initiated on VTE prophylactic dosing.

Certainly, thrombotic events can be an event that can initiate the conditions to decide to use anticoagulation. But as we've heard from colleagues before, this is, again, a very individualized benefit-risk assessment.

Dr. Ahsan: Great. thank you for that response. Let's move on, Dr. Koroshetz, if you can ask your question, please.

Dr. Koroshetz: Karl, I just want to return to two things that I think you said, make sure I got it right.

But the first is that the respondents, whether you responded or not, did not correlate with the change in the factor Xa activity. But the second thing was that there were more thrombotic events in the respondents than the non-respondents. Is that correct? Those two things correct? Dr.

Kasamon: No, I don't believe we said the second statement. Maybe Dr. Knoll could address the first one regarding?

Dr. Knoll: Yes, that is correct, regarding the anti-Xa. It was a similar reduction in both responders and non-responders that received andexanet.

Dr. Koroshetz: But how about thrombotic events? Were there any difference between the respondents and non-respondents?

Dr. Knoll: I don't know that we have that information, Dr. Kasamon?

Dr. Kasamon: You're right. At this moment, I don't have that information.

Dr. Koroshetz: All right. Thank you.

Dr. Ahsan: Not sure that we need a sponsor response to that. Great. Thank you. Dr. Wu, if you could ask your question.

Dr Wu: It seems to me that most of your positive data is essentially coming from your 12-hour hematoma volume, whereas pretty much all the other primary endpoints were negative, and maybe even worse with thromboembolism, with also some morbidity mortality issues.

So, my question is, besides the 12-hour time point, do you have post hoc analysis to see whether there's a difference in hematoma volume at 24 hours or at seven days? Because some of these patients, you're restarting the anticoagulation because they developed thromboembolism. So, besides that 12-hour endpoint in which you show a positive effect, is that hematoma volume, the positive effect maintained at later time points, do you have any post hoc analysis on that?

Dr. Knoll: I will defer to the applicant for that.

Dr. Ahsan: Before we get to that, for the applicant to respond to that, I do want to make sure that everyone is aware that that is a major part of the discussion point that we will be having in

the afternoon, which is whether hematoma volume change at 12 hours alone constitutes a clinical benefit.

Okay. So, if you wanted to provide some data, the sponsor can speak to that at this point.

Dr. Roe: Certainly. I'll ask Per Ladenvall to respond about details regarding scans performed beyond 12 hours.

Dr. Ladenvall: Thank you. So, can we ask the chair?

Dr. Ahsan: I'm sorry. What's the question?

Dr. Ladenvall: Can I share my screen?

Dr. Ahsan: Yes, I think you should be able to pull up a slide. Thank you.

Dr. Ladenvall: Thank you. As outlined before, the highest risk of hematoma expansion occurs within the first two, three to six hours and is captured by the primary endpoint assessed at 12 hours. However, we were asked by the FDA to provide additional imaging reports conducted as part of clinical care, which was not included in the protocol above 12 hours.

Considerable efforts have been done to generate this data, and we have been able to collect 89 imaging reports in 72 patients in the time point between 12 and 72 hours to assess the effect on delayed hematoma expansion in these patients. Two patients that not all had a hematoma expansion measured and identified already at 12 hours were noted in the imaging reports. So, they have language in their imaging reports indicating hematoma expansion, one in the andexanet group and one in the usual care group. That's indicating that delayed hematoma expansion beyond 12 hours is rare and should not impact our assessment of the data in ANNEXA-I.

Dr. Kasamon: I think we would just like to point out that we haven't had a chance to review those data. Thank you.

Dr. Ahsan: Okay, thank you. Dr. Koroshetz, if you want to ask your question, please.

Dr. Koroshetz: Can someone tell us what were the criteria for the ischemic strokes? Were they imaging? Were they clinical? Could be either one? And then I guess the one point to make is that if you have an MRS score, a bad MRS score, it may be very hard to see, you know, a stroke. But anyway, how are the strokes defined?

Dr. Kasamon: So, most of the strokes were defined with clinical and neurological deterioration. However, going to the fact that patients in the study may have impairment that's confounded or coming from the initial bleeding event, there were five cases where a new imaging finding of ischemia on brain imaging was the data leading to the adjudication of the thrombotic event of a stroke, ischemic stroke.

Dr. Koroshetz: Are these mostly CT scans or are they – They're going to see a lot of strokes.

Dr. Kasamon: So, it was MRIs and CTs.

Dr. Koroshetz: I mean, you're going to see MRI stroke in 30 to 40 percent of people, these little dots. I'm not sure if that's what they counted, but they wouldn't be necessarily clinically evident. You're saying that there was some clinical evidence of stroke in all except four. Is that correct?

Dr. Kasamon: That's correct, yes.

Dr. Koroshetz: Thank you.

Dr. Ahsan: So, we're challenged with time as we're starting to press up against the allocation we need for the open public hearing. Does the sponsor have an urgent data-driven response or input to this question?

Dr. Roe: Regarding the definition of ischemic stroke, I'll ask Per Ladenvall to provide a brief description of that.

Dr. Ahsan: If you could keep it brief, that would be helpful. Thank you.

Dr. Ladenvall: Yeah, I think it would be relevant to say that the adjudication charter had a comment on covert strokes. So, if there were no clinical correlates, they would not be counted as ischemic strokes. And that is a difference between the FDA classification and the predefined adjudication charter. Thank you.

Dr. Ahsan: Great. That's actually important input. Dr. Ott, is it a quick question potentially?

Dr. Ott: Yes, very quick question. I wanted to just ask about the usual care group and wanted to see what was the percentage of thrombotic events when the untreated patients were actually excluded and only patients with other treatments were included.

Dr. Kasamon: So, actually, the rate of TEs was numerically higher in the patients treated with no treatment, most likely a statistical issue due to the small numbers. I think we could have the applicant show that they likely have it easily available.

Dr. Ahsan: Does the sponsor have the usual care data stratified?

Dr. Roe: Yes, Rohit Narayan will respond for us.

Dr. Ahsan: Great.

Dr. Narayan: So, on the topic of usual care, there were 33 patients in the usual care group that received no active treatments to reverse the anticoagulation thrombotic event rate in this particular group was 12.1%. And this to us indicates the underlying thrombotic risk of the patients, but also thrombotic risks of the life-threatening bleeding and the clinical concurrent conditions that the patient experiences during hospitalization.

Dr. Ahsan: Great. I think we're going to leave that there now, as we need to break to allow the AV team to prepare for the open public hearing. This will also be our lunch break. So, we are meant to start at 1:10, right, Cicely? Promptly at 1:10, so we do have some time between now and then. So, we will see everyone there after the break.

Open Public Hearing

Dr. Ahsan: Welcome back. I think those on the West Coast, we grabbed a quick coffee. Hopefully the people on the East Coast were able to grab some lunch, and the folks in between were able to do what they needed. At this point I need to read the open public hearing statement. Welcome to the open public hearing session. Please note that both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Okay, with that, I hand it over to Cicely to run the open public hearing session.

Dr. Reese: Thank you, Dr. Ahsan. This is Cicely Reese speaking. Before I begin calling the registered speakers, I would like to add the following guidance. FDA encourages participation

from all public stakeholders in its decision-making processes. Every advisory committee meeting includes an open public hearing, OPH session, during which interested persons may present relevant information or views. Participants during the OPH session are not FDA employees or members of this advisory committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during the open public hearing session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate agency agreement with the statements made. In fairness to all OPH speakers here today, since this is a one-hour session, we ask that you please remain within your four-minute time frame. To assist in adhering to four minutes each, we are placing a timer at the lower left corner of your screen for each presentation. We greatly appreciate your cooperation. When I call your number, please unmute your microphone and open your camera, if you would like, and start your presentation. If you are not available at that time, we will come back to you after the other speakers have spoken. We will now begin with speaker number one.

Dr. AbuDagga: Thank you. My name is Azza AbuDagga. I am a health services researcher with Public Citizen's Health Research Group. We don't have financial conflicts of interest. Public Citizen's strongly opposes the supplemental application to convert the accelerated approval of Andexanet to full approval. Based on our assessment of the presented evidence, the post-marketing trial failed to verify a potential net benefit for Andexanet in acute intracranial hemorrhage subjects who are treated with Edoxaban or Rivaroxaban (phonetic). The trial showed a 12% difference in favor of Andexanet over usual care on a short-term primary efficacy endpoint. Measured 12 hours after randomization, this endpoint was a composite of three components. Although the difference, the 12% difference, was statistically significant, its clinical usefulness is questionable for several reasons. First, hematoma expansion, which was the

primary driver for the positive outcome, was actually measured just 12 hours after randomization, which is a much earlier time than guidelines recommend. Because no imaging data were collected beyond 12 hours, delayed hematoma expansion is unknown. Third, because hematoma expansion was measured as a dichotomous response, it does not fully capture the treatment effect on this outcome. The FDA had clearly relayed some of this information, at least, to the drug maker, who appears to have dismissed them. In terms of risks, 15% of the Andexanet-treated subjects suffered thrombotic events, compared with 7% of those who received usual care. This twofold increase was statistically significant. It is also clinically important because it was largely driven by brain thrombosis in the Andexanet-treated subjects, than the usual care subjects.

Although death rates were comparable between the two groups, the rate attributable to the drug was actually, due to thrombosis, was higher than twice in the Andexanet-treated group, than the usual care group. Other important methodological issues that were not mentioned in the briefing document may also suggest that certain aspects of the trial may have tipped the scales in favor of Andexanet. For example, whereas the safety analysis and sensitivity analyses for the efficacy endpoint included 474 subjects, the primary efficacy analysis excluded 70 of these subjects. It's not clear whether this exclusion favored Andexanet. Additionally, given that 79% of Andexanet-treated subjects received a low dose of the drug, the findings may not be generalizable to those who received a high dose. Moreover, the fact that 11% of the usual care subjects received no treatment, this also may have disadvantaged this group. In 2018, the clinical reviewers who reviewed the accelerated approval application for Andexanet concluded that the uncertainty regarding the clinical benefit of the drug, in combination with concerns about safety results in unfavorable overall benefit-risk profile for the drug. However, the FDA director

responsible for reviewing the application downplayed this concern, arguing that the risks are mitigated by the changes to the drug label. Six years later, there is still no acceptable evidence to support the benefit of this expensive drug, which was priced in 2020 at least $27,000 for the low dose in adults.

Therefore, we urge the FDA not to grant full approval for the drug. Instead, the agency should require a new optimally designed trial-powered justice, the clinical outcomes, and address the limitations discussed. Thank you for the opportunity to comment today.

Dr. Reese: Thank you, speaker one. We'll move on to speaker number two.

Dr. Goldstein: Hi, my name is Josh Goldstein. I'm an emergency physician at Mass General Hospital in Boston, and a professor of emergency medicine at Harvard Medical School. Conflicts, I will note, I have done consulting work for various companies, including AstraZeneca, also including CSL Behring, Octapharma, Takeda, Cayuga, and Pfizer. I'm not being compensated for my time here. I'm only sharing my personal perspective. As I've said, I've spent my career doing research on treating bleeding emergencies, including intracerebral hemorrhage. And I'd like to comment specifically on the question of whether an effect on hematoma volume change alone constitutes a clinical benefit. The key issue, I think, is that change in hematoma volume is a very accurate measure of bleeding in the brain. The bigger the change in hematoma volume, the more the patient has bled into their brain. And the question of what's the outcome after ICH, that's affected by many things, only one of which is the amount of bleeding. Factors that affect the outcome include age, baseline comorbidities, the location of the hemorrhage, and how much brain damage has already occurred before you ever see the patient. But the mechanism of action under discussion here, which is reversal of anticoagulation, it's not neuroprotection. It's stopping bleeding. And change in hematoma volume does measure that. In

general, stopping bleeding is good. In general, it's a clinically relevant outcome across a range of organ systems.

Now, in the brain, in general, the more bleeding in the brain, that's worse. But the link between more bleeding and worse neurologic outcome, it's probably stronger in some patients and weaker than others. So it does leave the research community this ongoing task, of figuring out which patients are the highest risk of the most bleeding, that's going to change neurologic outcome. I would say, as an emergency physician, I see people with all kinds of bleeding. For example, people don't think they're going to die from it, but they want treatment. They do come to the ED, and they want what's going to make the bleeding stop. For me, I do want to have treatments available for emergency providers that make bleeding stop. And for most organ systems, the outcome of 'did the patient stop bleeding' is a good clinical outcome, and one that is considered relevant for patients and providers. Whether 12 hours is the right timeframe to measure that, I certainly agree most trials in ICH use 24 hours as the timeframe. But I will note that most hematoma expansion, most ongoing bleeding, is happening in the first few hours after the event. So, you could pick a range of timeframes to measure ICH expansion, but most of the ICH expansion will have played out over the first 12 hours. There is a concern for a higher risk of thrombosis. And it may just be that for any hemostatic therapy we ever have for our patients, the more effective the hemostasis, the higher risk for the thrombosis. And that may be the price we're always going to have to pay for better hemostasis. Ideally, clinicians will have options available, such as Andexanet, so that in life-threatening circumstances, they can weigh the risks against the benefits, and quickly treat those who have the big opportunity to benefit. Emergency bleeding, and particularly in the brain, it can cause severe disability and death, and the more

options available for our frontline providers to improve hemostasis, the better. Thank you very much for your time.

Dr. Reese: Thank you. We appreciate your comments. Speaker three.

Dr. Jankowitz: Hello, my name is Brian Jankowitz, and I'm a cerebrovascular neurosurgeon at JFK University Medical Center in Edison, New Jersey. I'm a neurosurgeon who fell in love with treating blood vessels, of well over a decade ago, and the majority of my practice is focused on treating stroke. And particularly in the last five years, I've devoted much of my practice to treating hemorrhagic stroke. It's a frustrating disease to treat because of our limited treatment options, and if we look at the HA guidelines, the only level one evidence is to reduce blood pressure, but we still can't even agree on what blood pressure to reduce it to, and reversal of anticoagulation. So, these are the mainstays of treatment in a disease that has often defied any surgical benefit. Now, we did have a positive surgical trial to prove that we can help patients with hemorrhagic disease by removing the hematoma, but that was after 30 years of negative trials, and it's been frustrating to prove that treating an ICH leads to a significant clinical benefit. And I think it's simply because we don't have great outcome metrics, and because the disease is so onerous. And so, it doesn't necessarily surprise me that most trials looking at the treatment of ICH don't show a clinical benefit, and we simply need better surrogate markers of a positive outcome. I think that the staunching of hematoma expansion, or hematoma stability, is the single greatest, most objective predictive outcome metric of a positive trial. And I think it should reasonably equate to a positive clinical outcome.

We know that the vast majority, maybe 70% to 80% of hematomas expand. The majority of those hematoma expansions occur in the first couple of hours, and probably well over 90% occur within the first 12 hours. So, I think that the cessation of hematoma expansion within 12

hours is the metric I would use for current and any ongoing clinical trials moving forward. I think the benchmark of showing an improvement in clinical outcomes based on MRS may not be feasible at this point in time as, once again, we strive to achieve better outcome metrics. I also believe very strongly that hematoma expansion predicts a worsening outcome. I think we have excellent evidence to support that. I think we have softer evidence, but still something, I believe strongly in that stopping that hematoma expansion leads to better outcomes. But once again, we know that even down to one cc, one milliliter increase in a hematoma expansion, leads to worsening outcomes. So I have every reason to believe that stopping even very small expansions can lead to profoundly improved clinical outcome, as we're dealing with the most important real estate in the entire human body. And I also believe, as a guideline-driven physician, that we should be using specific reversal agents. I don't believe in using drugs that are given off-label to treat a drug. I believe in using drugs designed specifically to reverse an agent. So I believe that Andexxa (phonetic) is the only agent that I will use in my surgical practice to reverse a DOAC. If I am operating on a patient with a hematoma, I will only operate on that patient after giving them Andexxa, to immediately, and with longevity, reverse that hematoma. And it should be clear that I have not been compensated for this talk, and I have never been compensated by a pharmaceutical company. Thank you for your time.

Dr. Reese: Thank you. We will now move to speaker number four.

Dr. Peacock: Next slide. Next slide.

Dr. Reese: Mike, one second. I apologize. Can we go back to the OPH slide four? I need to warn the viewers that the following presentation contains graphic content. So, we can now move on to the presentation. Thank you.

Dr. Peacock: Thank you. Next slide. I'm Frank Peacock. I'm going to talk about reversal of misfortune. Next slide. These are my disclosures. I've got over 850 publications. I've been doing this 30 years, but I received nothing to do this, or no help in it. Next slide. I'm going to give you a series of cases. All of them have occurred in my practice, but none of their names or x-rays are of them, actually. This is Ms. Thornapple. She's somebody's mother. She collapsed, and this is her little tiny bleed. It's in her brain stem. The mortality of this is 50% of anticoagulant-associated intracranial hemorrhage. There's no acceptable amount of expansion that is good, and especially in the brain stem, because there's no room in the brain or in the skull. Next slide. So I'm going to give her an anticoagulant. My pharmacist says use PCCs because they decrease the PT, the prothrombin time. But by my calculation, and this is the first study done on that, there's only 17% decrease. Next slide. This is Stuart Connolly's trial, the prospective randomized standard therapy-controlled ADEXA trial. 94% decrease in anti-factor 10A activity. And this is at the 12-hour mark, which is a perfectly appropriate time for a drug that doesn't have very long half-lives. All the DOACs are short. And the standard of care is at 26.9%. So those are your choices. There are more increased thrombotic risks, but all these people who are on these anticoagulant drugs have a thrombotic risk. That's why they're on it. The 30-day outcome is absurd. These drugs last for a few hours, and that's all I need. Next slide.

This dude, standing in the corner, gets hit by a bus. You can see he's broke his right hip. His head CT looks OK. And so we thought, we won't do very much. We'll park him and tomorrow morning we'll fix his hip. Next slide. But about an hour later, one of the old ER nurses tells me I got to get in a room too. And old nurses, you listen to. So I run in there, and the guy looks like he's going to die. And I put an ultrasound on him. And you can see the red tracing around that. That's a blood clot around his heart. Next slide. So now I have to stick a needle in

him, an anticoagulant guy. I really want to stick a needle in the heart. That doesn't sound like a good idea to me. Do I want to use the 26% reduction, or do I want to use 100%? Next slide.

This is a case that the night team signed out to me. They're leaving the building. They want me to take over the case. I said, sure. Oh, we got a guy with a sore throat. No problem. Got a CT of his neck. What? Next slide. This is his CT. That's his epiglottis. It should look like a sheet of paper. It looks like a thumb. He's on an anticoagulant. He's bled into his epiglottis. And if he takes a deep breath and that closes off his airway, there's only one solution. It's a 'cric'. That means I have to slice his neck. And he's anticoagulant. Do I really want to slice his neck? Next slide. If you look on Google, what's a 'cric' look like? This is what they show. This is not what a 'cric' looks like. They are a bloody mess. This is a cadaver. It's what they look like when you don't bleed. Next slide. This is what they look like when you try to cut somebody who's on an anticoagulant, is that, the guy in the top is blowing air in there, and it's coming out through the hole I just made in his neck to stick the tube. And I've got to jam this tube down a bloody hole and try to find it. If I don't, he'll be dead. Next slide.

This is clinically relevant non-major bleeding. These people do not get reversed. They have a bruise on their butt. They don't get anything. They get sent home. Next slide. But this guy, who rode his motorcycle into a stop sign, do you really want me to use the 26% reversal agent when I got 100%? I've got to stick a tube down there. If I don't find his airway, he will die. Next slide. These are all the things American College of Cardiology says you should reverse immediately. Brain, spinal cord, heart, airway. They all need immediate reversal and not partly reversal. Next slide. I'm on a committee for American College of Emergency Physicians. Everything that has a reversal agent should receive it. And you can see they're all paired here. And last slide. Next slide. So this is everybody who is on the CTGT committee. And they're all

smart and extremely accomplished people. But I'll tell you, the challenge is this. There's nobody who uses them at daily practice like I do. These inhibitors, DOACs last a few hours. The inhibitors last a few hours. I just need a few minutes to keep that person alive. Thank you, and I'm done.

Dr. Reese: Thank you for your comments and thank you for your hard work in the ER. We'll move on to the next speaker, number five. Thank you.

Dr. Martin: Good afternoon. My name is Niels Martin and I am an associate professor of surgery at the University of Pennsylvania. I am also a trauma surgeon, practicing clinically every day. My comments here are my own, and not representative of my institution or anyone else. I will disclose that I have been a paid consultant, for both the current sponsor and actually the two prior owners of this drug as well. But I think what that has given me is an extremely robust understanding of both the mechanism of this drug and the patient population that it treats. I will fully respect the need for hard data any time we deploy any new type of science or medication or treatment to a patient population. However, I will say that that data needs to be clinically meaningful. And there was a lot of discussion around MRS scores. And I just, as a trauma surgeon, want to bring into the context of who we're treating, right? We are treating someone who is bleeding in that moment. And we need to stop that bleeding. And we need to stop that bleeding in the context of their anticoagulation. As has been said, that bleeding really needs to stop as immediate as possible. And generally speaking, bleeding does stop over the process of a few minutes to hours. The clinically significant bleeding absolutely occurs within easily the first 12 hours. That's probably the longest estimate of time.

And so, if you're looking at an endpoint at 12 hours, that will be the 95th percentile of inclusion of really where the significant bleeding is, especially if what we're talking about is

reversing an anticoagulant. Because at 12 hours, that anticoagulant is gone. And all other treatments and all other outcomes after that 12-hour point have nothing to do with this drug anymore. They have to do with all of the other aspects of treating the brain injury. And so really, if we're talking about reversal of anticoagulation and the outcomes associated with it, those outcomes are going to be the outcomes you see very very early, in terms of that bleeding. And so I think the 12-hour time point is actually highly effective. There was also another question outside of the clinical efficacy, as has been described in the New England Journal paper, about the use of anti-10-A levels. And I will say that in the clinical realm, we absolutely use anti-10-A levels, to facilitate the care of many different populations, not just those who need reversal, but actually we also use it in the opposite. We use it to dose titrate actually anticoagulation. So if we do it in that aspect, we can certainly do it on the reverse end. And I think that there is clinical validity in its use, and therefore, its measures, this population as well. In reference to the thrombosis risk, there is clearly a signal there, and something that we as clinicians have to pay attention to. But also, as has been said, I think that just means that we as clinicians need to be very, very selective of who we use this for.

We, every day in everything we do, balance risk versus benefit. Everything has a risk. We have to make sure that there is more benefit than risk. Selecting the appropriate patient population, those whose outcomes were absolutely going to change, are the people that we will use this drug on, and take that risk, and do everything we can do to mitigate that risk. But that risk is generally much smaller than the benefit that we perceive that we are getting, by adequately reversing their anticoagulation. That's a clinical decision point. And it's really hard to articulate in numbers. But I will tell you, as a clinician, that's something we do every day in literally every patient we care for. Thank you very much for your time.

Dr. Reese: Thank you for your comments. We'll move on to speaker number six.

Ms. Willman: Hi, my name is Elizabeth Willman. I will not be using video today. I do have slides. Could you show the first slide, please? Thank you for the opportunity to present to you today. I have no financial disclosures. I'm not receiving any compensation for my remarks today. I would like to share the experience of my mother's Aunt Carolyn with the advisory committee. She's not able to join the meeting today. So, I've got a few pictures of her. Aunt Carolyn's an incredible woman. She's a pillar of our community in Pittsfield, Illinois. She's a businesswoman and owner of a store in our downtown that's operated for more than 70 years. Her many achievements include being an inductee of the Senior Illinoisan Hall of Fame. She's an honorary lifetime board member of the Pike County Chamber of Commerce. She's a founding member of the Pittsfield Little League. She's been involved in the Illinois Home Extension, Rotary International, and many other organizations. Next slide, please.

I was blessed to develop a stronger connection with Aunt Carolyn when I moved back to my hometown of Pittsfield after graduating from college about 20 years ago. She asked me to join her at church on Sunday mornings and I was really able to spend a lot of time with her and get to know her better. In her own words, she's tried to figure out every problem that people had, and every time you could help somebody with a problem, they soon become help to you. At age 98, Aunt Carolyn was still working six days a week. One morning in January of 2022, she was brushing her teeth and noticed some weakness on one side of her body. She sat down and pressed her lifeline button. The ambulance came and took her to the local critical access hospital. When she got there, her symptoms were very subtle, but the physician in the emergency department that day was very astute and ordered a CT scan of her head, which showed that she had a bleed in her head. My mother was with her in the emergency department that day. My mother's a retired

emergency room nurse. She was filled with dread when she heard the findings from the CT. In the past, during my mother's career, bleeding in the head for a person of Aunt Carolyn's age, and with her medical history and medication list, which included Eliquis, that meant a catastrophic result. Fortunately for Aunt Carolyn, the physician providing her care that day knew there was an option to reverse the Eliquis and hopefully stop the bleeding that was happening in her head. Aunt Carolyn was flown to a larger hospital and treated with Andexxa. Next slide, please.

She did not experience any adverse effects after the Andexanet. Following her treatment, she spent a few weeks in the hospital, where she had some rehab and some physical and occupational therapy. She was then able to go back to her home, where she lived independently, resumed driving, and went back to work at her store. Aunt Carolyn's 101 years old now. She's had a few other health concerns since that time. She lived in a local nursing home. She's celebrated three more birthdays since this happened. Aunt Carolyn was able to have a party for her 100th birthday at her store. Hundreds of people traveling from several states came through to wish her well at her celebration. The local TV and newspapers came to cover the event. Another great niece of hers interviewed her for the newscast, and they talked about the challenges she faced as a woman in business 70 years ago. Next slide, please.

Aunt Carolyn is pictured here with a few of her great, great nieces and nephews. She's kind and gracious, the person many of us aspire to be. I'm grateful for the additional time my children and I have had to spend with her, and the memories my children have been able to make with her. My family and I feel that the time we've had would not have been of the same quality or duration without the availability of Andexxa. Thank you for your time today.

Dr. Reese: Thank you for sharing your personal story. We greatly appreciate your comments. We'll now move on to speaker number seven.

Dr. Patel: Good afternoon, committee members, and thank you for allowing me to speak today. My name is Nirav Patel. I'm a private practice neurologist, a vascular neurologist in Southern California. I'm also on the clinical faculty of UCLA Medical Center and UCI Medical Center. I've consulted with multiple pharmaceutical companies in the past, including the current sponsor, AstraZeneca, but I'm today speaking on behalf of myself. I'm not compensated for my time. And more importantly, I'm speaking as a caregiver. My story begins with my father, who like every other Indian, was diabetic, had his CABGNS (phonetic) at 57, is now having early dementia, ataxia from his neuropathy, and developed atrial fibrillation. At that time, his cardiologist and I felt that the DOACs were the best treatment for him, despite the risk of falling, despite the risk of not having a reversal agent. And that's what he was on. Unfortunately, my fears came true when one day he fell at home and sustained an intracerebral hemorrhage and subarachnoid hemorrhage. Prior to this, I'd worked very hard to making sure that Andexxa alpha was available, mostly for my father, where I was very biased. My father did receive Andexxa alpha, was discharged from the hospital, and I was very grateful. I understand that many people believe that the NEXA-I study was neutral, it was not positive, but I would like to remind people that this is an intracerebral hemorrhage, and most, if not all, intracerebral hemorrhages outcomes are measured in 90 days. This is a third day study. This is a hematology study and we should not be looking at outcomes. I think most of us would agree that that would not be appropriate.

The risk for thrombosis is real and understandable, and I would like to remind people that the AHA guidelines for ICH patients and using LVT prophylaxis is really important. And you'd be surprised that most hospitals don't follow this. In fact, in the study, close to only 70% of patients received the appropriate treatment. And if you were to use that, the risk for thrombosis was reduced by 50%. The alternative also, is, what are the risks for not treating? And we're

talking about life-threatening disease and mortality, and I remind people that it's not always the risk for the treatment, but the alternative is the risk of non-treatment. I'm a community neurologist and I look to my academic institutions for guidance in terms of best care. For me, as a vascular neurologist, I look at UCLA, I look at Stanford, and I look at Mass General. All three hospitals are using Andexxa (phonetic) alpha. Let me close by giving you some context. Many patients and families ask me, if this is your family member, would you use this particular medication? With the Andexxa, I would say yes, I would, and I did. And I'm thankful that my father received this medication. The importance of hematoma expansion and mortality truly outweigh the risk for thrombosis, which can be mitigated with appropriate treatment. Thank you for listening.

Dr. Reese: Thank you for your comments, Dr. Patel. We'll move on to speaker number eight.

Dr. Ganti: Hi, good afternoon. My name is Dr. Latha Ganti. I'm a board-certified emergency medicine physician, fellowship trained in vascular neurology. I've been in practice for over 23 years, and my area of expertise is acute stroke. My disclosures, I've participated both as a consultant and a speaker for several pharmaceutical companies including, Pfizer, AstraZeneca, and Cayuga (phonetic). I'm not being compensated for this testimony today. Thank you for inviting me to provide my perspective. So, when DOACs first came on the market, and many folks were switching over from Warfarin (phonetic) to DOACs, I was very worried that there was no reversal agent for it. As an ER doc, I deal with life-threatening bleeding on a regular basis. I remember thinking so many times, geez, I wish there was an antidote for these DOACs. Well, my wish came true when Andexxa came to market. Intracerebral hemorrhage, as everyone knows here, is the most devastating form of stroke. The incidence of ICH is higher with age and anticoagulant therapy. And as the population gets older, more and more patients are in DOACs.

And like Dr. Patel before me said, my dad was also on a DOAC. And so, for me, this is also, again, very personal. ICH disproportionately affects lower resource populations. So 50% of patients who suffer an ICH are dead at 30 days. So that means every one out of two patients that I see will not actually be here anymore. And that's an incredibly devastating statistic. I always tell my students and residents to kind of pause and think about that. Of those who do survive, about half of those suffer a disability that prevents them from going back to work or leaving independently. So, just to give everyone a perspective of what happens in the ED.

So, when somebody comes in and they're a stroke alert, a whole team comes down. We get vital signs, labs, CT, history. Somebody's doing the checklist for TPA eligibility. Somebody's calling the family. There's a whole bunch of people there ready to see if it's an ischemic stroke so they could do something about it. The minute the CT comes back with the hemorrhage, it's like hot potato. Nobody is there. Everyone vanishes. All those people who were in the ED before, bam, everyone's gone. It's just you. So, then I, the ER doctor, have to call neurology. I have to call neurosurgery. Nobody wants the patient. Neurology says give it to neurosurgery. Neurosurgery says make the patient DNR. And then I have this patient and I have nowhere to send them. Thankfully, on August 11, 2022, the first time the American Stroke Association came out with some specific guidelines for ICH management. And I'm so grateful. These guidelines recommend specific antidotes for patients on specific anticoagulation therapy. And so, this is great because prior to that, we used to basically have PCC that we would use indiscriminately. And we know that the efficacy of PCC for DOAC-associated ICH is about as effective as the exam. So two main things to consider about a brain hematoma, like how big is it, and how fast is it expanding?

So, size of a hematoma is measured by volume. And so the larger the volume, the worse the prognosis. Next is the rate of hematoma expansion. Is it like oozing or is it gushing, right? Oozing is better, I suppose. We can categorize hematomas using the scoring system. And based on the number of points on the scoring system, we have a rough prediction of what is the rate of expansion and what is the predicted mortality. So, as an ED doc, I mean, forget like 90 days, 30 days, 12 hours. I care about the minutes, right? And I think we've had a few other ER docs here say the same thing. I care a lot about controlling the rate of hematoma expansion early, because the best neurosurgeon, the best interventional neurologist in the world, is still dependent on my hyperacute timeframe and the hyperacute care that I provide. So, if I don't do a good job in those first several minutes, then they can't do anything, because the patient will not even get to them.

So, I feel very responsible for attenuating this bleeding as quickly as I can. And then I guess before me would be the pre-hospital personnel. So as the ED doc, if I can act promptly to contain the hematoma, then the amazing neurologists and neurosurgeons can do their work. But I have to get the patient to them first. The Adnexa-I trial demonstrated hemostatic efficacy and reduction in median anti-factor 10A (phonetic) activity. The safety analysis showed an increase in the rate of thrombosis when compared to usual care. And this makes total sense. If DOACs are anticoagulants, then the reversal agent is going to be an anti-anticoagulant or a procoagulant.

Dr. Reese: So, Dr. Ganti, we appreciate hearing from you and your compelling testimony, but we're going to ask you to come with your concluding statement.

Dr. Gant: Okay. So, I basically just want to thank you for giving me the opportunity to make my remarks. Thank you so much.

Dr. Reese: Thank you so much, especially for your heroic work. And we'll move on to speaker number nine.

Mr. Fanikos: Thank you. Thank you for including me. My name is John Fanikos. I'm a pharmacist by training. I spent 40 years at Brigham and Women's Hospital in Boston. I was involved in the Anexa-IV trial. I've been involved with our antithrombotic stewardship program and published a number of articles surrounding anticoagulation safety. I retired about a year ago from the hospital. I have now joined the Vascular Network, which is a not-for-profit patient advocacy group for those suffering from clotting and bleeding complications. I have served as a consultant to a limited number of pharmaceutical companies, including AstraZeneca, but I am testifying on my own behalf and I'm not being compensated. I want to draw on my experience while I was at the hospital, and I think you'll hear some common themes. When I was there, we were administering Andexanet about once a week, so about 50 patients per year. When you looked at those 50 patients, about 40 of them had intracranial hemorrhage. And even with the best of our care, about 40% of those patients who came to our facility bleeding ended up dying. When you looked at that population of patients, what we found was that the vast majority of them were being transferred from smaller hospitals, from community hospitals, from rural centers, from urgent care centers, for advanced care. And when you communicated with those centers, you found out that there was a hesitancy to treat patients with a reversal agent like Andexanet. There was confusion on what was the best therapy, and it created treatment delays. And in fact, today, if you go to Google and you type in Andexanet, you'll find that the computer offers you alternative products that are not approved for reversal of drugs like apixaban or rivaroxaban. So, my point here is, is I think full approval may mean that many smaller rural

hospitals may be able to start therapy earlier, rather than waiting for it to be delivered at an academic medical center.

You've heard this already, that hematoma expansion typically occurs in the early or first few hours. It quickly leads to neurologic deterioration and raises the risk of death even with as little as one milliliter. And it's almost impossible to predict those patients that present to you, as to which ones will have hematoma expansion. So, what I'm asking is for the FDA, it's one of the most powerful organizations in the world, to provide full approval so that we can clear up some of the confusion, some of the hesitancy that appears with treatment. We can smooth out the silos and fragmented care that's being delivered, and offer patients a possible better outcome. So, better choices to promote better practice. And that's my testimony. Thank you for including me.

Dr. Reese: Thank you for sharing your comments. They're greatly appreciated. We'll move on to speaker 10.

OPH Speaker #10: Excellent. Thanks so much for the invitation. I appreciate it. I am a cardiologist working in Pittsburgh. I have been a speaker for AstraZeneca in the past. Certainly not being compensated for being here today. So, I come at it from a slightly different angle than the other speakers. As a cardiologist, I see tons of patients who have diseases that put them at risk for thrombosis. AFib, DVT, and so what do I do? Well, the cornerstone of therapy is prescribing agents that reduce the risk of stroke. And initially, when I first started training, that was a lot of vitamin K antagonists. And now we've transitioned to using DOACs. And why did we make this change? We made this change because DOACs are safer and work better. In fact, the guidelines recommend this. It's a class one recommended therapy. And because of this, there are millions of patients, probably over 5 million today, on these DOACs. And thankfully, we are seeing excellent results. We are seeing that the real-world data of these therapies result in patients

having less strokes and less bleeds. When we think about the intracranial hemorrhage rates of vitamin K antagonists, it's about 0.8. These drugs, it's 50% reduced, about 0.3. So, the bottom line is this is an excellent number. The problem is there are millions of patients on these DOACs. And a small risk of bleeding means there's still going to be lots of bleeds. And that's why all the other speakers, the ER physicians and neurosurgeons, are quite busy. And patients ask us, in particular me, when I prescribe an agent, is this safe? And what can we do if something happens? And I think it is imperative to us that we have a strategy involved to reduce this risk of bleeding, and to manage the bleeding when it happens. So, my job is to prescribe the right drug, use the drug appropriately, and to have a strategy involved if they do have the catastrophic bleed. And that is why I am pretty passionate about Andexxa. It's the first and only selective 10A inhibitor. So in my experience, anecdotally, I have certainly seen excellent results, as the other speaker said. My take on the clinical data is such that, you know, when you look at healthy volunteers or sick patients, it lowers 10A levels. I think that's indisputable. Clearly this is seen, and it happens quick and happens safely. I think the clinical trials clearly show hemostatic efficacy, which is a surrogate marker, but certainly an impressive marker in sick patients. When you look at the thrombotic risk, you know, I deal with these patients who have a thrombotic risk already. I know that's real. I think you need to pick and choose and find the appropriate patients. But really, when you look at that thrombotic risk, if you start them back on appropriate anticoagulation, it does mitigate that risk. And that is, I think, an important message for prescribers, that this drug can be used safely. I think there's real-world data that is supportive of this product as well. And what do the guidelines say? Well, the guidelines really recommend using specific reversal agents. And I think that's what's valuable here, is, you know, when we start thinking about the error of evidence-based medicine and using medications that work, you really want to stick to specific

reversal agents. And that's what Andexxa does. So, yes, I am passionate about the therapy. And I think as a prescriber that provides and prescribes a lot of these DOACs, we need to be able to have a strategy to reduce it. And that's where Andexxa comes in. And again, thank you for your time today.

Dr. Reese: Thank you for your comments. We really appreciate them. We'll move on to speaker 11.

Dr. Concha: Good afternoon. My name is Mauricio Concha. I am a vascular neurologist and director of Sarasota Memorial Comprehensive Stroke Center in Sarasota, Florida. I've been involved with Andexanet alpha since Adnexa-IV trial, serving as a side PI, and later on in Speaker's Bureau. I'm also currently working on a study funded by the sponsor to understand the obstacles of door-to-needle reversal times for all anticoagulation agents, in patients experiencing intracranial hemorrhage. I'm testifying today to share my perspectives based on over 30 years of experience in neurology. However, I'm not being compensated for my time.

Let me bottom line this. Let's put the fire out and let's do it timely. If I have a patient who is bleeding profusely and who is on any anticoagulant, among the first things I have to do is block the anticoagulation effect, no matter what follows. That's the first thing I have to do. Therefore, we would like to use the most specific antidote that neutralizes the anticoagulation as fast as possible. This premise applies whether the management that follows remains medical or becomes surgical. In fact, arguably, the aim is to contain the hematoma from expanding so that the clinical effects are mitigated and perhaps surgery can be avoided altogether. It is clear that intracranial hemorrhages are associated with high morbidity, including a mortality risk that is about twice that of ischemic stroke. Anticoagulation at the time of the hemorrhagic event more than doubles the mortality risk and the risk of hematoma expansion. It is important to consider

that the natural history of hematoma expansion is steeply time-dependent, with most of the expansion occurring within the first three hours from the onset of symptoms, and it remains one of the few potentially modifiable variables in intracranial hemorrhage management. Moreover, as has been said before, as little as one cc increase in hematoma volume will increase the chance of death or clinical disability by 10%. Studies show that Andexanet alpha reverses the apixaban and rivaroxaban's anticoagulation effect within two minutes after the end of the initial bolus. This is clinically meaningful. Management of intracranial hemorrhage should be a timely process from the moment the patient hits the emergency door. And Andexanet alpha does its part. To me, it is clear.

ANDEXXA-I trial results support the use of Andexanet alpha. Nevertheless, it is important to acknowledge the 30-day safety findings regarding thrombotic events. Importantly, however, these complications appear to be modifiable with the early reinitiation of anticoagulation, and observation also supported by findings of ANDEXXA -IV. 2022 American Heart Association and American Stroke Association guidelines for the management of patients with spontaneous intracerebral hemorrhage recommend an early start on anticoagulation prophylaxis once hemorrhagic stability is established. This practice may mitigate the thrombotic adverse events observed in ANDEXXA -I and has been successful in my institution. ANDEXXA -I was designed to evaluate hemostatic efficacy at 12 hours and change in anti-factor 10A activity during the first two hours of treatment with Andexanet alpha compared to usual care. In practical clinical terms, this means efficacy mitigating hematoma expansion, a critical determinant of poor outcome, and rapidity in the onset of action. In life-threatening hemorrhages on apixaban or rivaroxaban, Andexanet alpha is the best option to help put the fire out. Thank you.

Dr. Reese: Thank you very much for your testimony. We greatly appreciate your comments. We'll move on to speaker 12.

Dr. Dobesh: Hello and thank you for this opportunity. My name is Paul Dobesh. I should have some slides. There we go. My name is Paul Dobesh. I'm a professor at the University of Nebraska Medical Center at the College of Pharmacy. And I work in the world of anticoagulation as an anticoagulation pharmacist for over 20 years. I've worked with a number of pharmaceutical companies over those years, and I am not being compensated. I should like to also mention that I have been an author on the ACC consensus statement for the reversal of oral (phonetic) anticoagulation, but my comments don't reflect them. But the guideline does recommend the use of Andexxa as the preferred agent for reversal of these patients. And it's because of the data. That's why it gets used clinically. It's because of the data. You know, many comments I noticed in the discussions before about, you know, the lack of difference from an ANDEXXA -I in the modified ranking scores, or the mortality.

The study was not designed to look at those. The study was designed to look at hematoma expansion, and that's what it did. And it was stopped early, even making those other endpoints more difficult to analyze. If I can go to my next slide. My other experience, I've published a number of papers on Andexxa over the last several years. One of them is this. We've conducted the largest real world clinical trial. The largest real world evidence study, of almost 4,400 patients and patients with rivaroxaban and apixaban major bleeding, getting either Andexxa or a four factor PCC. Our main outcome here was in hospital mortality. If you go to the next slide. And what you can see here is that, in this data, that the blue represents patients. Actually, that is reversed. Sorry. The blue represents patients getting Andexanet alpha. The red is patients getting four factor PCC. And you can see, basically, when you plug these numbers into

the multivariable logistic regression model down at the bottom, that patients getting Andexxa alpha was associated with a 50% lower odds of in-hospital mortality in everybody, almost a 50% lower odds in in-hospital mortality in patients with intracranial bleeds. And even though GI bleeding mortality in the hospital happens significantly less often, there was still over a 50% reduction in odds for in-hospital mortality in patients getting Andexanet alpha versus getting four factor PCC. If we go to the next slide, then, you know, I understand that there's been a number of these observational studies that have been done. But remember that real world evidence is basically complementary to clinical trials. It answers questions that clinical trials can't. Studies like ANDEXXA -I are not designed to look at mortality. They're not nearly large enough. And I understand that there's a number of these types of studies out there, but just think about, you know, our data is much different than what else is out there.

Many of the studies that are out there are limited by small size and scope, where our data had basically 4,395 patients from 354 U.S. hospitals across 42 different states. Not a single hospital, not a single system. Many studies do not have time from last dose. 85% of ours-- we had time from last dose in everybody, and 85% were in the last 18 hours. So we knew we were reversing something. Most studies have limited data on GI bleeds. We have over 2,500 GI bleeds. And many studies do not try to make statistical corrections, which is probably the Achilles heel of these types of data. But not only did we deal with multivariable logistic regression as our primary analysis, we also did a sensitivity analysis with propensity score weighting. Because what if one of our models was not accurate? And thankfully, we found consistent results with both. And once again, if you look, our data looked at in-house for mortality, not hemostatic efficacy, and showed this reduction. I would also just like to comment, there was a statement made earlier about cost. And that was a little bit erroneous. The cost of the

drug is over 55% lower than what has been previously stated, which makes it actually a much more attractive agent for use in these patients. Thank you very much for your time.

Dr. Reese: Thank you very much for your comments. And we'll move on to the last speaker, number 13.

Ms. Alexandrov: Hi, I'm Anne Alexandrov. I'm a professor at the University of Tennessee Health Science Center. And I'm testifying on my own behalf as a nurse practitioner and member of an acute stroke team that responds to the emergency department to provide care to patients with intracerebral hemorrhage. Although I've consulted with pharmaceutical companies, including AstraZeneca, I am not speaking on their behalf, nor am I being compensated. Intracerebral hemorrhage, as you've heard, is the most devastating form of acute stroke. And stroke practitioners aim to prevent bleed expansion because this is a significant determinant of disabling life-threatening outcomes. That risk of bleed expansion is front-loaded, meaning that within minutes from arrival to the emergency department, we have to work very fast to control it. And in a patient on factor 10A inhibitor anticoagulation, that risk is extremely high for expansion. But often hospitals lack access to Andexanet because the accelerated approval is not viewed as definitive. A recent case highlights this, with a very vibrant, active 70-year-old woman on factor 10A inhibitor anticoagulation that was brought to her local stroke center for sudden onset of severe headache and right arm weakness. Her physician, like many anticoagulant prescribers, was under the impression that all hospitals carry Andexanet for anticoagulation reversal. However, this unfortunately is not always the case. A small brain bleed was noted on the patient's CT scan, and the telemedicine stroke physician recommended the emergency physician immediately give Andexanet. However, the hospital pharmacist informed him that the drug was not on their formulary at their small community hospital.

Therefore, off-label, four-factor PCC concentrate was given instead. But as expected, it did nothing to control hematoma expansion. So, what started out as a small bleed with minimal disability ended up expanding to a large hemorrhage that ultimately resulted in the patient's death. Sadly, this case is not unique. While Andexanet carries a risk for thrombotic events, I'd argue that this is because it works. It stops anticoagulation, putting back into play whatever risk factors existed that caused the patient to be placed on anticoagulation in the first place. However, experienced stroke teams know how to monitor stability of the brain bleed, and start early anticoagulant prophylactic measures, usually within 36 hours of admission. And this minimizes risk, as you've already heard, including in the ANDEXXA -I data.

I strongly encourage the FDA to provide full approval for this life-saving agent so that hospitals' formularies will include Andexanet, and not tie our hands in the treatment of these cases. Intracerebral hemorrhage does require a bundled care approach, but rapid reversal of anticoagulation with agent-specific antidotes is among the most important of first steps to prevent hemorrhage expansion. Both patients and anticoagulant prescribers expect the antidote to be widely available, but without full approval supporting formulary inclusion of the agent, there's little we can do to prevent severe disability from this very deadly form of stroke. And there's a very real risk that the use of highly effective 10A inhibitor agents may decline due to lack of an antidote and patient concerns. Thank you very much.

Dr. Reese: Thank you, Ms. Alexandrov, for your comments. They're greatly appreciated. We are grateful to each of you for sharing your thoughtful remarks today with this committee and with the agency, and for taking the time to be with us today. We invite each of you to watch the remainder of today's proceedings via the YouTube link provided earlier, and also on the

committee's webpage. Thank you again so much. We will now proceed to the next portion of our meeting. Dr. Ahsan, I'll turn the meeting back over to you. Thank you.

Dr. Ahsan: Great. Thank you, Cicely. And I'd like to thank all of the Open Public Hearing speakers. It was very insightful and informative to hear from many of the doctors that actually use, or are on the front lines, of this treatment. So, we have a break now. And when we come back, we'll have the committee discussion. So we will reconvene at 2:20 Eastern time, 11:20 Pacific time. And so, we'll see each other then, and enjoy your break.

Committee Discussion

Dr. Ahsan: Great, welcome back everyone. Appreciate your continued presence in this meeting. The committee members, this is where we will do our heavy lifting. So for the next hour and a half or so, we are going to discuss the points that the discussion questions, the FDA has posed of us. Let's see. So the key thing for this next session is that it is really meant to be a robust and dynamic conversation among the committee members.

If we have specific points of clarification from either the FDA presenters or the sponsor's, we can ask them, but hopefully we have the information and the data we need in order to have this conversation that we want to have the next hour and a half. There is no voting question. The purpose of this discussion is that the FDA will be taking arduous notes, and it is for them to gather their insights and to get a sense of the recommendations from this committee. So I think the first thing we're going to do is read the questions for the committee. So if you want to present that slide. Is that going to be up? There we go.

So we have two questions. The first one is about the efficacy and the second is about, really, the benefit to efficacy ratio. And it's a little bit broken out so we can talk about different

elements in a robust manner. And then we'll have opportunity to summarize our viewpoints at the end. So question number one. The primary efficacy endpoint in ANDEXXA-I was met with largest treatment effect from among the three endpoint components consisting of the change in the hematoma volume at 12 hours. Other clinically meaningful outcomes, neurological status at 24 hours and overall mortality, for example, were not different between the two arms. MRS at day 30 was worse in the Andexanet arm. Discuss whether the treatment effect on the study's primary efficacy endpoint constitutes a clinical benefit to patients. So that's the general discussion point.

We can again summarize before we move off of this question, but let's try to actually address the three bullets below that one at a time. We'll first talk about the hematoma volume, then the neurological additional assessments, and then finally the role of anti-factor Xa in the reduction. So let's start with does an effect on hematoma volume change at 12 hours alone constitute clinical benefit? So as we move on, it would be good for everyone to raise their hand in the chat function. I can recognize you, and then we can speak one at a time, and then we can move forward from there. So great. Dr. Morrison, if you'd like to start us off.

Dr. Morrison: Yeah, thanks. You know, we heard often this morning that better hemostasis leads to better outcomes, but it wasn't really evident in the numbers from the clinical trial that patients that were treated with the Andexanet have had worse outcomes in terms of neurological function, death, and severe adverse events. And yet all the physicians that we've heard from urged us to grant full approval, suggesting that there's some advantage to Andexanet beyond what was being measured in the clinical trial. And I'd be interested in hearing from the physicians on the panel about what precisely that is.

Dr. Ahsan: Yeah, that was a great point. There are a lot of ER docs in the open hearing session that pointed to wanting to use this as a tool in their box as they were treating patients. Are there clinicians here who can speak to that? Great. Dr. Wolfe.

Dr. Wolfe: You can hear me, I suppose. So we've heard several times that one cc increase in volume increases the risk of death or dependency by 5%. There's other metrics too. And so there's different formula, one's an ABC over two formula that measures the dimensions of the ICH and the number of cuts on a CT scan where you see it. And then you can actually figure out what the total brain volume is. And from a percentage standpoint, this was drilled into my head years ago. When you're at 2% for an ICH, you've got a chance, moderate disability, maybe a little bit better than that. Once it goes to 4%, so just a 2% increase, you're in a vegetative state or dead. So if this agent at 12 hours where most of the expansion occurs has a benefit from the standpoint of not allowing that hematoma to increase more than 35%. So in the example, I just gave two to 4%, that would be 100% increase. But if it's doing that, I think other studies would suggest the outcome should be improved. Wasn't seen, but I can just provide some background there and perhaps some other clinicians could add to that or refine what I just said. I hope that made sense.

Dr. Wolfe: Well, Dr. Wolfe, can I ask you for a little bit of clarification there? Do you think that the markers for clinical outcome are not sensitive enough to detect that positive change?

Dr. Wolfe: The AE data is very nuanced. The causes of death are somewhat all over the map. From my reading, hemorrhagic deaths were somewhat less with Andexanet. The thrombotic deaths were a little bit higher with Andexanet. Taking a step back from the deaths, if you're looking at strokes, yeah, there are a lot more strokes with the Andexanet. From what I can gather, and this is following from what Dr. Koroshetz was asking about, it seems about one third of the strokes were silent. They said five. There were 14 total. So just trying to put that all together, I

mean, it's difficult. But yes, I think actually what was captured is not really fully reflecting the thrombotic risk alone. It's nuanced. There's other stuff in there, but yeah, I hope that explained it a little bit further.

Dr. Ahsan: That's helpful. Let's make sure that we kind of stay on mute until it's our turn to speak. Dr. Ratan, you're next to have your hand up.

Dr. Ratan: Yes. I think it's important to distinguish studies that establish a correlation from studies that establish causality. I think the majority of studies, at least as I understand them, establish a causality between a correlation between expansion and worse outcomes. And there are some studies, as they pointed out, that suggest that manipulating a volume directly can lead to improved outcomes. So the way I sort of see this is their effect on hematoma volume is essentially evidence of target engagement and a test of the idea that a change in hematoma volume actually will lead to decreased mortality and improved outcomes. And they didn't see that. And that's further complicated by the fact that they see these increase in thrombotic events, which could be nullifying any potential benefit that they would see from affecting hematoma volume alone. And so, I really think that it doesn't seem like a change in hematoma volume, especially because it was so relatively large for patients who are untreated, is enough as a primary endpoint, because really, ultimately, the measure of integrated benefit in the nervous system is either function or the ability to avoid mortality.

Dr. Ahsan: And can I ask you a question to follow up on that, which is, is this a situation where, you know, mitigating the change in hematoma volume is necessary, but not sufficient?

Dr. Ratan: Well, I don't know if we can answer that at this point. I think that one could say that if there weren't increased thrombotic events, and because of the fact that you're seeing other things, one could, it seems to me, that that's possible, but it's also possible that this is not the particular drug to test that idea because it increases those thrombotic events.

Dr. Ahsan: Yeah, and so thank you for that comment. And maybe as we go through the discussion, you know, the information that comes to us through the public hearing is a little bit unvetted, not to question their credibility, but it's unvetted. And so, as someone who's not in the field, it would be good to hear from the hematologist. There was one doctor that referenced that there was compelling scientific information, independent of this one drug, that the hematoma volume is directly related to negative outcomes. So kind of understanding whether that in a cleaner study is actually true, if someone has some insights on that, that would be helpful. Maybe that's something that we can think about as the discussion progresses. Thank you, Dr. Ratan.

Dr. Ott. Yes, thank you. I have two comments here. One is that I was struck by the word later outcome, and we have, I think, a 30-day outcome, but the 90-day outcome was not measured. I did not fully understand why it was not included. I think there was some logistic things. But I think I wonder, and I would very much welcome the expertise of the panel to understand whether there's a big difference between 30 and 90 days, and whether, you know, that is going to be relevant.

And then my second point was that I was also struck by when the sponsor presented saying that they think that their drug was applied later than it's usually applied, especially in the United States, two hours versus one hour after onset of bleeding, and whether that also could mitigate some beneficial effects, because the volume might be already so big that even if you stop it, the damage is basically done.

Dr. Ahsan: Thank you, Dr. Ott. Great comments. Thank you very much. Good questions. If we could hold off on the discussion of MRS at day 30 versus day 90 until we get to the second bullet, that would be great. Want to close out the conversation on the hematoma volume first. I think also before we move off of this question, I will bring back that two-hour versus one-hour treatment window as well. Great questions. Dr. Koroshetz.

Dr. Koroshetz: Hello. Can you hear me okay?

Dr. Ahsan: Yes, we can.

Dr. Koroshetz: So I was just going to say that, you know, this is a little bit deja vu. NIH in early, mid-2000, 2008, that came out in New England Journal of Medicine, did a study of activated factor VII for ICH. This is not people who are on DOACs. This is just ICH in general. It showed that the increase in volume at 24 hours was 26% in the placebo, 18% in the treated group, but no clinical benefit. So what we're doing now is we're going back and we're doing the trial again at a shorter time window with the idea that that was a four-hour window. And as was just mentioned, the thought was you need to go earlier. So it is possible that outside of the if it's in practice, and I think that in that prospective data that they presented, I think they mentioned that the treatment in the real world is actually occurring really quite quickly, that the benefit might be further increased. I would say in terms of the hemorrhage volume, I think, you know, I think if it was not for the thrombotic events, one would expect that you would get better outcomes by decreasing the growth of the hemorrhage. I think that seems pretty clear from all I know about intracerebral hemorrhages.

In the trial, the activated factor VII, we saw the same problem with increased thrombotic events, which, so I think we're caught between the balance of the good and the bad here.

Dr. Ahsan: Thank you. Helpful comments, helpful comments. Any other opinions about how the hematoma volume change at 12 hours is really connected to the clinical benefit? I think, you know, there's a sense that it was expected, but between the TEs and other metrics, we're not seeing as clean a correlation there as we would want. Dr. Ahuja.

Dr. Ahuja: Thank you. So I'm a hematologist that treats bleeding and clotting disorders. I'll be in pediatrics and young adults, so I don't see the older population as much, but I do see a lot of patients who are on DOACs. I can tell you from a hematologist perspective, if a patient is bleeding on a anticoagulant, the first thing you need to do is to reverse that effect. And they obviously andexanet does that, looks like pretty well. The decrease in volume, I'm not a neurologist, so I don't know what, I mean, we heard that every milliliter counts. So I do believe that. However, we need to also look at what is the alternative here. There's no alternative here. I mean, people use PCCs for reversal of these agents without any approval in that category either, right? And that actually complicates matters because a lot of physicians will use PCC the way they want to use PCCs. And I think that might be indirectly contributing to harm in this patient population. So once you have an approved drug in this category, I think it's only beneficial for the patient population in general. It makes the lives of physicians easier. It makes insurance approvals easier for other things. So I think collectively, I mean, obviously reversing it, decreasing the volume, if a study designed in a different manner makes you a clinical benefit, it did not in the traditional sense here. But I think in my mind, at least it met the goals it was supposed to do, which showed it reversed and it decreased the volume. So thank you.

Dr. Ahsan: Great. Thank you, Dr. Ahuja. I'm sorry, too much time in California. You mispronounced your name. Let's see. So I think that that's actually an important point that maybe we can layer on here, which is when we look at the neurological status, is that really what the

drug is meant to do? And is that a fair expectation that we're looking for as we are using this in an emergency room situation? So just for the clinicians to think about, I only pose the question. I don't have those answers. Dr. Kindzelski.

Dr. Kindzelski: Thank you. Actually, coming back to the actual question, it's interesting that the hematoma volume change is the primary outcome for the clinical trial and everything else is secondary. So clinical benefit is pretty much a secondary outcome for the clinical trial. We were presented today by multiple people. I think neurologists should provide the actual response to how hematoma volume change constitute clinical benefit. But from a hematological point of view, it clearly shows that the reversal agent works, and it does exactly what it's supposed to do. I just wanted to, even though FDA puts together everything in one question, I still want to separate it. The purpose of the drug and the neurological aspects of these specific conditions. So just a little bit of information to think about.

Dr. Ahsan: Yeah, no, exactly right. I think that that'll be an important part, especially to talk about when we talk about bullet two, which is, are those really outcomes that were meant to be measuring? I just want to make sure that I have this correct. And, of course, if you all can double check what I'm saying, but I do think that the outcome was measured on three metrics. It was both the hematoma volume, the NIHSS score and whether rescue therapy was used in the three-to-12-hour window after that. Just, I think that that's how they viewed the overall outcome. But what they found was the hematoma volume change was what really drove that significant difference that they detected. Is that correct?

Dr. Kindzelski: Yes, you're correct. But relevant to this question, I focused on hematoma volume change.

Dr. Ahsan: Yeah, no, no, absolutely fair. Absolutely fair. Dr. Ortel.

Dr. Ortel: Right, just to kind of follow up on both of the last comments. If we're looking at this as the drug is designed to reverse the anticoagulant, I think that yes, it's very effective at doing that. The problem becomes one is we're trying to tie it into all of these other outcomes that, as they described, have other contributors to why there might be bad outcomes in this patient population. One problem with it is the thrombotic events. Clearly, if we reverse the anticoagulant and then we allow thrombotic events to occur, we've created a problem. We do have it on formulary at our institution. We do have it approved that the neurosurgery or neurology folks can use it for intracranial bleeding in cases where we've got anti-Xa activity documented. We can turn the assay around very quickly. And they do have problems partially because of the fact, I think there's just very inconsistent application of strategies to reinstitute the anticoagulant afterwards to try to address that piece of this. And they kept mentioning the fact that they know how to implement VTE prophylaxis, which is fine and dandy, but the problem is arterial events. So VTE prophylactic dosing may not be the best strategy to use to try to drop these thrombotic events. And they did have a paper in the series of papers that they gave us about the size of the bleed and the correlation with or outcomes. So that does suggest that if we can control the size, if the trial is designed correctly, they might be able to see that change in the clinical impact. But then if you could do something to abrogate that thrombotic risk or drop the thrombotic risk at the back end, that might make it much more attractive.

Dr. Ahsan: Yeah, thank you, Dr. Ortel. We'll definitely be speaking about the benefit to risk profile in the second question, which isn't visible here, but I'm talking about the safety aspects and the TEs in particular. And so another question for the clinicians, again, I don't know the answer. It's not my field, but a point that you brought up, Dr. Ortel, which is if this, if Andexxa

really to reverse that anticoagulant, are the TEs really a reflection of over effective reversal? Is that part of the issue, which is that's why we're getting the TEs, right? Because we have the inhibitor to the inhibitor.

And then the second question, which I think has come up a couple of times, which is the sponsor said, well, we know how to handle these thrombotic risks, but as we make it approved and it's used in a wider landscape, does everyone have that same expertise to handle those TEs? Dr. Ortel, could you help me understand that a little bit? Am I being clear? Yeah, so I do think they did show some data about the fact that this also does impact an anticoagulant piece of the pathway, the TFPI. So it may not be that these thrombotic events necessarily are just the fact that you've reversed the anticoagulant and you have a person who's already procoagulant. You may also have done something to TFPI to kind of tip the scales a little bit to increase the risk. I don't know if we understand that piece of what Andexanet is doing as well as we probably would like to know, let me put it that way.

But that would be the one way to think about how it might be impacting thrombotic events afterwards. And I'm sorry, the second part of your question was?

Dr. Ahsan: Well, as we move to approval and there's a wider use of it, the same care mitigation strategies, right?

Dr. Ortel: I think that you're gonna have to have, at given hospitals, you're gonna have to have sources of expertise to help drive the decision-making and to help move that forward. When this drug was first introduced here, we did have it given to some people that, in retrospect, you would think were too prothrombotic to begin with, probably shouldn't have given it to them. And they did have a thrombotic event afterwards. So I do think there has to be, these cases have to be

individually evaluated and thrombotic risk assessed before you really place somebody at that potential risk.

Dr. Ahsan: And evaluating what your management capability for that risk, great. Thank you so much. Sorry, Ms. Eggimann, if you wanted to ask your question or make a comment.

Ms . Eggimann: Hi, thank you, Dr. Ahsan. I wanted to see if he thinks if that's okay. I don't intend to speak a lot, but I do have a few remarks that I wanted to make. And in particular, I raised my hand because you did ask the question about what is the actual clinical benefit that we should look at. So hopefully my remarks will help address that. And I want to clarify that I'm chief regulatory officer at Tessera Therapeutics. And my remarks are really from the regulatory perspective. So I hope it will be helpful for the advisory committee members.

So first of all, I wanted to comment the agency for bringing this topic to advisory committee today as the small increase of thrombotic events in the indexer group compared to the usual care arm should be discussed. And at least from my perspective, it's important for clinical experts to share their opinion and hear multi-stakeholder opinions. So I do hope that today's meeting is going to help the agency make a decision with regards to whether it would be appropriate to convert Andexxa's accelerated approval into a full approval. For industry, I believe that, and I believe that's true for patients and for the agency as well, the ability to leverage accelerated approval to bring products to patients earlier to meet a significant unmet need for serious conditions is critically important. Accelerated approval means that FDA may grant approval upon determination that a product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. There are other parts to the definition, but that is the main form for, the main basis for accelerated approval. And for drugs that are granted accelerated

approval, post-marketing confirmatory trials are required to convert to full approval to confirm that the data collected using the surrogate endpoint correlate with a meaningful clinical benefit. So in our case today, in 2018, FDA agreed with the sponsor in what is called a post-marketing requirements that-

Dr. Ahsan: I'm sorry to interrupt. This isn't specific to the discussion questions.

Dr. Eggimann: I'm getting-

Dr. Ahsan: Okay. To the specific question of either hematoma volume or the neurological status. Ms. Eggimann: I guess I want to-

Ms.. Eggimann: Yes, I will answer the first question that's underlined from my perspective. And I just wanted to give adequate background for people to follow the logic if that's okay. So in 2018, the FDA agreed with the sponsor in a post-marketing requirement that the large phase four randomized clinical study that the sponsor should conduct to confirm the clinical benefit of index describe and verify the hemostatic effect of Andexxa. And that patient should be assessed with the NIHS and CT scans as well as MRI at 12 hours post-randomization. And the agency also required trial assessment that included occurrence of safety events all to be observed at least three days for immediate occurrence or at least 30 days with weekly interval for delayed occurrence. So I think it's important in this conversation to understand that demonstration of clinical benefit for Andexxa means demonstration of hemostatic effect, not long-term neurological effects. So the sponsor conducted the phase four study as agreed upon with the agency and they met the primary endpoint. And this primary endpoint did confirm superiority of hemostatic efficacy compared to usual care. In addition, the sponsor is committed to updating the

package insert to reflect the risk of thrombotic events. And I'm sure they'll collaborate with the agency to make sure physicians are well-informed.

The long-term outcomes are outside of the scope of this phase four study. So I think that's just important as we answer these questions. And then it is, I think, important from my perspective and I think from the industry perspective that there is precedent for other approvals of anticoagulants and all the prior reversal coagulation agents approval were based on coagulation parameters. And if needed, the applicant could provide more information on this. I'm almost done.

So from an industry and regulatory perspective, I think it's important not to change the goalpost in terms of the evaluation of Andexxa phase four as it is important for all stakeholders to have confidence in the PMR process and for the agency to be consistent across product of the same class as well as across sponsors developing products in the same class. So I would like to respectfully point out that from a regulatory perspective, response to question one asked by the agency should be yes, meaning the primary endpoint of Anexxa I is a clinical benefit. That is why the agency required the applicant to conduct the study to confirm the benefit of Andexxa. So I do appreciate FDA's second question and very much look forward to the discussion on question two as to me, this is the most important question based on the existing data is the benefit risk confirmed to be positive? And as I said earlier, experts should really opine on that. I will not comment on that. But I did want to make this regulatory point about how to answer question one. And then lastly, I wonder if real-world evidence would be a good way for the sponsor to answer some of the questions that are raised today regarding longer term outcome or the optimal time to reintroduce the tachyregulin treatment. The sponsor pointed out this morning that they have real-

world evidence evaluations ongoing. So it might be interesting for the applicant and the agency to discuss this in the future. Thank you very much for letting me finish.

Dr. Ahsan: Great, thank you. I do think that that's an important point whether we've moved the goalposts and whether we've moved them to an area that is no longer relevant for how we're meant to use this. But I do think that the FDA wants to make a clarification. So I want to recognize the FDA room. I'm not sure who's going to speak.

Dr. Fashoyin-Aje: Yes. Thank you, Dr. Ahsan. I'm the Director for the Office of Clinical Evaluation in OTP. Thank you so much for the robust discussion so far. I wanted to provide a few points of clarification. The question really before the committee is to opine and provide your perspective on the data that was submitted. We are not asking the committee to opine on whether or not the trial was designed to evaluate certain outcomes. We are asking the committee to opine on whether the quantum of data that has been submitted in this application and presented today constitutes clinical benefit. We are also not asking for a regulatory perspective on the application. Our questions are purely on the clinical data submitted in the application.

I also want to remind the committee that converting an accelerated approval to a traditional approval requires demonstration of clinical benefit. That is why we ask for more data. And so while we're not asking for a regulatory opinion on the application, I just want to just provide that as a clarification that the way that we are defining clinical benefit is as a measure of how a patient feels, functions and survives. That is the benchmark. That is the requirement and it applies to every product that we approve. Thank you.

Dr. Ahsan: Great, thank you. It's very helpful to have the FDA make sure that we stay within the guardrails. And to her point, let's stay really focused on the bulleted questions. I think many of us, myself included, started to stray. So that's very helpful.

Dr. Koroshetz: Can I ask a clarifying question?

Dr. Ahsan: Yeah, go ahead, Dr. Koroshetz.

Dr. Koroshetz: I'm confused by one thing and that is the approval is for a drug to reverse the DOACs. It shows that it can do that. The question is the indication in which was chosen for this trial where it's not clear that it helped people. Are those really separate? So for instance, in the worst of all possible worlds, could you approve the drug and say it's really not, it's not for intracerebral hemorrhage. Is that possible here? So it did what it did, but it didn't help this context of this syndrome of bleeding. But, you know, GI bleeding or bleeding around the heart, things like that are different. Definitely does reverse the DOAC.

Dr. Fashoyin-Aje: Is that question for me? Dr. Ahsan, is that?

Dr. Ahsan: Yes, that's for you, please.

Dr. Fashoyin-Aje: Okay. So if I understand correctly, Dr. Koroshetz, your question is, how did we approve the drug if we did not?

Dr. Koroshetz: No, no, going forward, is it possible that this is an outlandish idea, but is it possible to prove the drug reverse of DOACs, but not in intracerebral hemorrhage?

Dr. Fashoyin-Aje: The approval, oh, I see. Well, that's a different question. That's a different question entirely. And I don't think that the sponsor has data for reversal of DOACs agnostic to

the type of bleed. So we're speaking specifically about intracerebral hemorrhage today. And that is the indication for which accelerated approval was granted.

Dr. Koroshetz: No, I thought it was granted for any hemorrhage due to DOAC. Isn't that true? Like trauma?

Dr. Ahsan: Yeah, the language seems to be life-threatening or uncontrolled bleeding.

Dr. Koroshetz: Yeah, so there's lots of different life-threatening bleedings.

Dr. Fashoyin-Aje: Yes.

Dr. Koroshetz: This one happens to probably have been their best choice to go after.

Fashoyin-Aje: Yes, this study studied this particular population, but the indication is for bleeding. That's correct.

Dr. Koroshetz: Okay, so could you get approval for the indication, but have, say, a black box warning that the data for intracerebral hemorrhage is not sufficient to recommend? You know what I mean? So you're separating the indication. I think this is what Dr. Ortel was saying. The indication could be approved for reversing, but the data saying in the black box warning is that the data does not recommend it for intracerebral hemorrhage. So you separate out this type of bleeding from the others.

Dr. Ahsan: My suggestion would be that how the FDA takes our insights to implement the change moving forward, we will leave for them because that is not an appropriate decision to be made live.

Dr. Koroshetz: I see, okay, thank you.

Dr. Ahsan: But maybe those are things that we can articulate in the discussion to help put some ideas of how to move forward. Is that fair, Dr. Fashoyin-Aje?

Dr. Fashoyin-Aje: Yes, that is. Thank you so much. I was hoping to sort of get the conversation focused and not expand it. So yes, I appreciate those comments. But if there are different perspectives about what additional data may be useful, we certainly are interested to hear some of that after you respond to the specific questions that are before the committee. Thank you.

Dr. Ahsan: And we're going through time quickly because of a dynamic conversation. That's wonderful. We only got to bullet one. You know, you can nuance in bullet one comments as well. But let's start to focus on bullet two, which is should neurologic status at 24 hours, MRS at day 30, and overall mortality be incorporated into the assessment of benefit of Andexanet. So, Dr. Wolfe, if you want to go on camera. Oh, did we lose Dr. Wolfe?

Dr. Wolfe: Okay, I'm here. So this is going to be a slight extension to what Dr. Koroshetz just mentioned. But regarding that second question, and I know a lot of us were looking at the MRS at baseline. I'll say no to answer that question. But I want to qualify it because we have this disconnect of the hemostasis and these ultimate clinical outcomes. If they had restricted the entry criteria to patients coming in with ICH, who had an MRS of four to six, so not the better ones, but four to six, I don't think we would be sitting here because they showed a slide where that group seemingly did show clinical benefit versus the standard of care arm. I mean, the percentages were quite different. We didn't see statistics all over the place. So there's something happening with those zero to threes. And I'm only speculating on why that may be. But, you know, based on what really the primary goal was, I don't think those items, well, status to 24

hours, perhaps, but some of those longer term, I question whether that is fair to include those fully. But again, I qualify it with that MRS division. All right.

Dr. Ahsan: No, I also noted that, which was the MRS for those that have baseline four to six. So if you want to go back, it's on slide 32 of the FDA presentation, if you wanted to look at that more carefully while we're discussing. Dr. Morrison.

Dr. Morrison: Yeah, so, you know, if I look at all of the data, I don't see a clear clinical benefit because you get a 12% improvement, absolute improvement in hemostasis and a 9% increase in severe adverse events, many of which were severe adverse events that led to death. Having said that, what we're hearing from every physician that has talked to us is that they want to see this approved as though the only thing they really care about is having something to stop the bleeding. And so what I wish I had a better understanding of is whether if it's the case that these longer term measurements, like risk of death and neurological functioning are not that important to the physicians that are going to use this, then there's a case to be made for not including those things as endpoints in the clinical trial and really just focusing on hemostasis.

But I've not heard somebody clearly articulate the case for why it would be that we wouldn't, why it wouldn't really matter whether there was improved neurological function or other longer term benefits, you know, as noted, which seem likely to be driven by treatment related adverse events, the increase in thrombosis being most notable.

Dr. Ahsan: Yeah, that's a great point. I mean, I think the difference of the balance of the hematology versus the neurology, right? And whether that neurologic status at the later time points, is that relevant to what it is that the sponsor is proposing it be used for and how the at least the ER docs in the open public session were articulating how they wanted to have that in

their toolbox as access for something that they could implement. Does that capture what you're saying, Dr. Morrison, which is?

Dr. Morrison: That's right. And if there are some indications for which these longer-term measures don't really matter, I really wish somebody would articulate the case for that.

Dr. Ahsan: Yes, right. So the impact on the MRS is that how important is that? So Dr. Ratan, I'll let you.

Dr. Ratan: Yeah, so I would just say that. And I think this maybe aligns with Sean's comments. And that is that. There is a huge amount of spontaneous recovery that goes on in stroke, hemorrhagic stroke, and it's highly asynchronous. So being able to detect changes in neurologic status at 24 hours or even at 30 days are going to require many, many patients to detect an effect. But the rationale for stopping bleeding acutely is that reducing that bleeding will ultimately have some effect on how the patient feels, functions or survives. And if they've shown that they can reduce the hematoma volume, but there's no effect on mortality and actually an indication that some of the outcomes that they're measuring are actually worse, then it's not clear what the mandate is to stop the bleeding. And I think that's what Sean was saying in a different way. And I would say that these are if you were going to measure MRS, I mean, ideally, you do it at 180 days because that's when patients plateau. There are a lot of events that go on between the acute setting and 180 days. So mortality becomes an outcome that can be measured relatively early with and has sort of is kind of finite as an outcome measure. So the fact that they're not seeing any of those, it would, I think, makes it difficult to understand what's the rationale for reducing the bleeding. In this way.

Dr. Ahsan: Yeah. And so that's also great points. I think that that was also raised before about the relevance of the different values of the MRS and whether the assay is too noisy at day 30 versus later on is also, I think, part of the question about the timing of that. So potentially, MRS might be valuable, but maybe at a later time point than at day 30. Dr. Kindzelski, please.

Dr. Kindzelski: Thank you. Just coming back to the actual question, and I think it depends if the goal is to assess the drug as the reversal of the DOACs, it shouldn't be utilized. If we are looking on how the drug is treating intracranial bleed in general, which is a very complex process. Yes, we need to look at 24 hours, 30 days, and maybe 180 days as recommended by neurologists.

Dr. Ahsan: Great. Thank you. Dr. Wu.

Dr. Wu: So I guess to me as a practicing cardiologist, and we do see these patients who are on these medications for AFib mostly, and they do bleed probably in a different setting than the ICU with intracranial hemorrhage. My question to me is that obviously the drug works, right? It decreases the numbers and decreases the hemostasis, but yet we're confronted by lack of clinical data that we saw, and also maybe increased thrombosis. And that's where we're really, really stuck at. And I think the CHAT-GPT will tell us that that's negative data, but we as humans will probably say that, well, there's a lot of stuff behind it, and we need to adjust our decision making for it. But my question is, could it be possible that the researchers or the company just dose it way too high? I think the low dose is 400, the high dose is 800, and they dose it way too high so that it causes all these thrombosis issues that we're concerned with. And had they gone with the lower dose, you would have given them the reverse effect without all the other complications that may have led to some of the increased death.

Dr. Ahsan: Yeah, thanks. We'll probably address dose again as part of question two. But one thing that I wanted to actually ask you, Dr. Wu, specifically, because you had talked about this, is how do you think about if we could start moving to bullet three, the anti-factor XA reduction as an assessment tool? I think you had some thoughts about that during the question-and-answer session.

Dr. Wu: Yeah, I think I asked them several times to see whether there's a correlation. I think ideally the correlation would be that if we have lower anti-factor XA activity, it would correspond to better hemostatic efficacy. But my understanding from their response is that they didn't see a correlation. But I think we're really stuck with the thrombosis issue that may be indirect marker that the drug is working towards causing all the thrombo reversal. So that's why I asked the question, could it be possible that they dose it way too high?

Dr. Ahsan: Yeah, great. Does the sponsor have a comment directly to what Dr. Wu was asking? I see your hand.

Dr. Roe: Yes, I would like to reference and share a slide if possible. We presented information that shows that there is a correlation between the reduction in anti-factor XA activity and hemostatic efficacy as shown in this slide. So directly to one of the questions that Dr. Wu had, I'd like to just raise this point. And this analysis was done adjusting for other things that contribute to hemostatic efficacy, such as lowering blood pressure, such as the baseline hematoma volume and the baseline anti-factor XA activity before reversal. So just wanted to be clear, we did show a correlation here that was positive and statistically significant.

Dr. Kohn: Thank you. Dr. Kohn.

Dr. Kohn: Just want to make some comments, but it's a real regulatory dilemma here. They met their primary endpoint, but the primary endpoint really wasn't designed to look at how a patient feels, functions or survives. And so we're now talking about all these other indications of that, but that wasn't their primary endpoint. And I think, as we've said, in this setting, it doesn't seem to provide a clinical benefit. And the MRI findings and volume is just really a surrogate marker. But yet, based on what all the clinicians who use this drug said, this drug is important for other indications and other purposes. And so I don't know how there is a route to get it to remain approved if the decision is made that it wasn't shown to be effective for this primary endpoint. So I don't know the answer, but I think that's the problem.

Dr. Ahsan: Yeah, for sure. I mean, I think we'll discuss that a bit more as part of discussion question two. So in terms of these metrics and how they relate to clinical benefit, are there any more comments that people would like to make before we start talking about the risks?

Dr. Koroshetz: I would say, I think the only thing I'd say is that in terms of hemorrhage, things, the patients generally get worse. And that's often due to either the toxic effect of the blood or the edema. So some people even after 24 hours will get worse because edema comes into play. If someone at 24 hours, what you're trying to get at is neurologic status that's most related to the hemorrhage itself. You wait later, then it gets even more complicated.

The MRS at day 30 is much more stable. Things are usually done by that time, but you're not getting into the recovery phase as Raj said. So I think neurologic status at 24 hours is a good indicator for effect of the drug on reducing hemorrhage size increase. But it also is capturing the ischemic events that are coming really fairly quickly after the drug is given. A lot of the strokes are coming, it's day one, but it could have happened eight, 10 hours after the drug was given. The

MRS at day 30, I think is not unreasonable. It'll change, but I think it'll be more proportionate at day 90 to day 31. So that's what I would add to that.

Dr. Roe: So Walter, we see cell death within six hours from the toxic blood products.

Dr. Koroshetz: Yeah.

Dr. Roe: In an animal, I don't know how that relates to a human. So I don't know if you can parse the hematoma volume versus the other events that are happening contemporaneously. And I would not agree with the idea that the 24 hours is going to tell you much to parse those different aspects of the pathophysiology of ICH based on our work and others. But if you did see a historic doubling the hemorrhage size in the first 24 hours, that's going to get picked up on the neurologic status, right?

Dr. Roe: Well, it all depends. Like if you're sitting in the middle of the internal capsule, it might. But if you're sitting medially in the striatum, you may not see it much.

Dr. Ahsan: Okay, I'm actually going to skip a bit and get to the FDA because usually they have a point of clarification.

Dr. Fashoyin-Aje: Yes, thank you, Dr. Ahsan. I wanted to have the opportunity to show a slide that illustrates or provide some information around the hemostatic efficacy correlation with anti-factor Xa activity that percent changes if that'll be helpful to the committee.

Dr. Ahsan: Yes, for sure.

Dr Fashoyin-Aje: Okay, Dr. Knoll will walk us through it.

Dr. Knoll: Thank you. Can we pull up slide 31 from the FDA presentation? So this just shows the median anti-10A reduction in both responders and non-responders in the andexanet

arm. And both were equal. 95% reduction were seen in both responders to the hemostatic efficacy outcome at 12 hours. In both, again, patients that responded as well as did not respond. So there was no difference when looking at this reduction in anti-1Xa activity and hemostatic efficacy.

Dr. Ahsan: Dr. Knoll, that's very helpful. But can you help us contextualize that with the data that the sponsor showed where they tried to do some corrections and showed a correlation?

Dr. Knoll: I do not have that data on this slide, but sorry, Lola.

Dr. Fashoyin-Aje: Yeah, I can just, I can just say, you know, I think a lot of these analyses are obviously exploratory analyses. So we just also have to interpret them with some caution because the studies weren't really specifically designed to evaluate this correlation. But we did want to show it's kind of descriptively that if you look at clearly this product is associated with a mean change and decrease in the anti-factor X activity. So we're not debating that, but we're not seeing any difference between people who are responders as measured by the hemostatic efficacy endpoint versus those who do not respond. And so I don't know, I can't comment on the sponsor's analyses. They were not, you know, shared with us specifically to sort of redo. But again, you know, they may be adjusting for factors that are not, we don't know if they're sort of comparable across study arms. So we do just need to interpret that with caution.

Dr. Ahsan: Yeah, and I think, you know, to just reiterate what you're saying, which is we do see this reduction in activity and that's very clear, but we see no connection to that with the clinical outcomes and the hemostatic efficiency, as you show very clearly in this slide. I'll give just a very quick moment to the sponsor to speak to, again, that slide, I think that you showed a few minutes ago.

Dr. Ro: Thank you for the opportunity to respond. I'll respond briefly on the responder analysis. And we recognize this is a subgroup defined after randomization. And those patients who respond and achieve hemostatic efficacy in the usual care arm are potentially a healthier group of patients whose bleed stopped without specific reversal. So therefore, these types of responder analyses may be inherently biased against the Andexanet arm. So we think it's important to consider that aspect when understanding these analyses. Additionally, to get to a point that Dr. Koroshetz was raising on the 24-hour neurological outcomes, if I could share a slide, please, to respond to that. I think we have some data that inform the second bullet of the first question. And here, when we look at change in NIHSS greater than or equal to seven at 12 hours, that is accentuated in terms of the treatment-related differences at 24 hours, as shown here, with a 7% absolute reduction at 24 hours and a 5% at 12 hours. So we just wanted to add that data to the discussion. Thank you.

Dr. Ahsan: Great, thank you. I just do want to reiterate what was mentioned a moment ago, which is the data is complicated. And these studies were not necessarily designed for the clear correlations that we're asking about. And so we do have to take all the data as a whole and be cautious about interpretation. Dr. Lund, if you have a comment really briefly before we move on to question two.

Dr. Lund: Yeah, I was looking at slide 31. I'm very intrigued by that because for me, what it shows is that the patient's not receiving the drug had about a 30% reduction in Xa activity. And they did just as well with survival overall. So that kind of says to me that you don't need 95% reduction. But I'm wondering if I'm thinking about this too simply. There were comments about dosage earlier about whether or not the dose was too high. But I mean, that's the thought that comes to my mind is that this amount of reduction is not required for hemostatic control.

Dr. Ahsan: Yeah, I'll just add one point. This is overall. This is an assessment of hemostatic efficiency or efficacy. And there was one comment in the open public hearing about talking directly about the ability to control hematoma volume and, you know, a 20% versus a twofold change. And, again, we got to take that for what it is. That's not vetted data. That's not a vetted speaker. But there was that comment, I think, aligned with what you were saying. So great. Thank you very much for that comment. Let's move on to question two. We can still talk about the metrics in that context. Great. So discussion question two, for which we have still about a half an hour of robust conversation was an ANNEXA-I demonstrated an increased incidence of thrombosis, 14.6% versus 6.9%. And thrombosis related deaths at day 30, 2.5% versus 0.9% in the Andexanet arm compared to the usual care. Are the serious risks of Andexanet as demonstrated in that next one acceptable in the indicated population and in the context of the clinical efficacy demonstrated in an ANNEXA-I? So I think this is where we're getting to basically risk to benefit ratios or benefit to risk ratios. Who would like to start us off on this? If I could ping Dr. Wu to talk a little bit about dose, your dose comment. If you could reiterate here, that would be great.

Dr. Wu: I think it gets back to what Dr. Troy Lund just mentioned, right? So, I mean, if you look at the slide that shows respondent, non-respondents, both of them minus 95% reduction, it tells you the drug is working very, very well. And that's what it's designed to do. But then it's causing all this side effects as shown here in question number two. And maybe some of these side effects and translate into the increased mortality, albeit not statistically significant. That's why I asked the question and it's possible that the patients with those, I mean, the patients with those way too high and could, instead of a 95% reduction, could a sweet spot be say at 50% reduction, right? The control group was about 30% reduction. For some reason, the control group

had a reduction already. Could a sweet spot be about 50 to 60% reduction that you could slow down the bleeding or stop the bleeding without causing all the subsequent thrombosis here. And then you have to chase after these thrombosis again by anti-coagulating the patient. Yeah, that's what I was getting at.

Dr. Ahsan: Great. Thank you.

Dr. Koroshetz: I think that the, you know, more complication in the high dose, was that FDA think that was statistically significant?

Dr. Ahsan: Does the FDA had, did you stratify the data between low and high dose and mortality or the TEs? Dr. Knoll, perhaps you had that.

Dr. Knoll: Yes.

Dr. Kasamon: We actually have a backup slide, which shows that, let's see what chart it is. So slide number 66 of the deck. And I'm sorry, this is Karl Kasamon. So for this analysis, the patients in the usual care arm were basically subdivided into two groups using the same criteria for dosing as was used to dose high dose versus low dose. And then we looked at TE rates and mortality by those doses. And I think what it, for instance, shows is that the bottom left box of each table has the numerically highest thrombosis, 20.8% for high dose patients on Andexanet. And same thing on the right with a 39.6% mortality for high dose Andexanet patients. And then you can see the other corresponding boxes being low.

Dr. Ahsan: So am I reading this correctly? That actually the higher dose had more incidence of TEs and higher rates of mortality, right?

Dr. Kasamon: Yes, that is correct.

Dr. Ahsan: So that goes directly to what Dr. Wu and some others have intimated, which is has the dose been, would it serve us to further optimize the dose in order to decrease these SAEs for this drug? And along those same lines, I want to, in addition to dose, bring back Dr. Ott's question about the timing of treatment between two hours and one hours. And does that play into it at all? So I see you have a question, Dr. Tifft, but maybe we can address this dose and timing at this point. Is there anyone who'd like to comment on that?

Dr. Fashoyin-Aje: Drs., may I just really quickly comment since we're the ones presenting this slide? You know, I think that what this shows is that we have some hypotheses here that may need to be further tested. So I just want to again caution that we have a smaller number of patients who received a high dose. And so I would be, you know, I think I'd be remiss to not just sort of caution as to the fact that these are exploratory analyses that may indicate something, but they're definitely not definitive. So just want to mention that.

Dr. Ahsan: Thank you. Great. Again, thank you for keeping us on target. So if I go back to the question, which is, are the serious risks of the Andexanet as demonstrated in ANNEXA-I acceptable in the indicated population in the context of clinical efficacy? I think some of the insights from the committee is, well, do we need to further understand that risk and how that is different for different populations and different treatment regimes? I don't think we need to pontificate more on that. As the FDA mentioned, that's a much deeper question that requires a lot more discussion offline. But it seems like, are there clinicians that would agree that that's something that's worth exploring further and that we can leave that to the FDA to do?

Dr. Koroshetz: Yeah, I would agree.

Dr. Ahsan: As a non-clinician, I'm very reluctant to take a position just trying to summarize. Okay, Dr. Tift, if you wanted to ask your question.

Dr. Tifft: Sure. And this is sort of the flip side of dose, I guess, which is the patients themselves. I think in the FDA slide set, slide 48, that had all the individual thrombotic events. I think there were at least two patients, 31 and 32, that had looked, to my eye, more than one thrombotic event. And I don't know if there were other patients there as well. And I guess I would ask the question, is there something, you know, all these patients are included in this trial, but they're obviously different. I say this as a clinician, as a geneticist. And is there something about some patients in this trial that predispose them to more thrombotic events than others? And if so, is it possible to ferret that out so that you would know not only how to adjust the dose, but which patients might be at higher risk?

Dr. Ahsan: Yeah, I mean, I think the sponsor did present some data showing that the medical history in ischemic stroke and myocardial infarct had an impact on those effects as well. So Dr. Koroshetz, if you wanted to comment.

Dr. Koroshetz: Can I just say that this is a really high-risk group. 81-year-old was the average age. And if you intracerebral hemorrhage, you get, because you have lifelong hypertension and you have, you know, one vessel breaks, but none of them are healthy in many of the cases. Or you have congocephilic angiopathy from Alzheimer's changes. So I would say the comorbidities in this population are extremely high, which would be very different, say, than someone who is, had the GI bleed, doesn't have vascular disease. These people all have vascular disease. They're going to be at high risk for any kind of procoagulant event happening in their blood vessels to actually end up with ischemic conditions.

Dr. Kasamon: Yeah, and in addition to that, the increased ICP is going to decrease the perfusion globally, which will also contribute to ischemia.

Dr. Koroshetz: And they're having, as I mentioned before, for a reason we don't quite understand, when you do an imaging MRI in these folks, in a large percentage, you see strokes. It's a very stroke-prone population.

Dr. Ahsan: So yeah, this would be great to kind of really get into that, which is, at the end of the day, if you took it in its totality, the question is, can we put the question back up? And the AV folks put the question back up. Are the serious risks acceptable in the indicated population and in the context of clinical efficacy? That's the crux of the question.

Dr. Koroshetz: But what's your indicated population? If it's reversal and any life-threatening bleed, that's a whole bunch of different populations. This one is only inter-cerebral hemorrhage. That's a very specific population. So that's what I'm trying to figure out. What is the indicated population we're going to make our decision on?

Dr. Ahsan: Right.

Dr. Ratan: But it does, I mean, I think one of the things to think about, and I think this gets back to the comments about dose, is, is the lowest dose use the most homeostatic dose? And would that be the dose you would choose for any of these other indications where you might apply the drug?

Dr. Ahsan: Ms. O'Sullivan-Fortin.

Ms.. O'Sullivan-Fortin: Hi, thanks. I guess for me, question two hinges on, am I to impute all of the TEs just to the ANDEXXA? Or is it just returning a sick person to their natural state

before they were on the meds that their clinicians felt were required for them to maintain their health? And perhaps, you know, not only are they returned to their natural state, but it's enhanced by the fact that they're going through an intracranial hemorrhage and the body's response to that. I just, you know, this is not a study of 10,000 people where we can really see all the effects. I wonder if this is still relatively small numbers. And when we're looking at that slide 31 or 32, whatever's been keeps going up, those are even smaller numbers. So I just, it's hard for me to parse this out, especially in considering 12 of the 13 respondents to the OPH are clinicians who seem absolutely desperate to use this and to have this and Alexander number 13 said there is an increased TE risk because the drug works. So should we not put them in a position to use this, add this to the toolbox? Are we just making too simplistic a conclusion here? Not a clinician.

Dr. Ahsan: Yeah, no, I agree with you. I think, you know, you and I have been on several of these meetings and this is the first time I've seen so many clinicians in the open public hearing really asking for this drug. Let's see, Dr. O'Brien.

Mr. O'Brien: Hi, thank you very much. Just following up with Professor Koroshetz and the discussion that's there, I find both questions actually hinging on definition. So if one is to define clinical benefit as to the overall of stopping a bleeding, then because it's uncontrolled bleeding, then clearly we heard in the passionate pleas of an ER doctor, it stops bleeding and we need to stop that bleeding.

If we define it as more looking at the neurological deficits or the MRS scores, that becomes a whole different issue with it from a patient perspective, because in many cases, myself included, it's not so much deaths, even though we looked at death being double in that of the data, it's actually MRS scores of four and five and being a burden upon society and families and what quality of life is. Those are the questions that patients look at. And it's similar to here

on what the professor was bringing up in terms of how do you define indicated population? It's clear to me, again, if the question is stopping bleeding and those ER people that are coming in with brain bleeds, then yes, I want this. It's clear to be that.

However, it sort of reminds me of opioids. When the indication of opioids was to eliminate pain or treat pain, it was clear that it did that. But unfortunately, then we left with two decades of side effects that have impacted patients more than anything else that we can find. And I get fearful that in terms of this and Andexanet that are we, because a large population of this, if it's beyond brain bleeds, intracranial hemorrhaging, what we're talking about the vast majority, 88% are atrial fibrillation patients that are on there because they fear stroke. That's why they're on this is because they fear stroke. Are we now exposing a very large population to a use of a drug that may in fact damage them or harm them? I think that's a very legitimate question to ask. So if we get defined it to say, listen, what we're talking is about is intracranial bleeding in this population that had intracranial hemorrhaging within people that have, that are bleeding, that are on apixaban or whatever the other drugs are, then yes, okay, we can do that. But I think we have to be very careful as we expose it outside of that population.

Dr. Ahsan: Thanks, that's very helpful. Before I get to you, Dr. Ott, let me go back to the FDA because it seems like they might have a point of clarification.

Dr. Fashoyin-Aje: Thank you, Dr. Ahsan, and thank you for the discussion. Again, I just wanted to provide us clarification since the question did arise regarding the indicated population. I wondered if I could clarify. So Accelerated was granted to Andexanet for the treatment of patients who are treated with rivaroxaban and apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. So as has been brought up by several members of the committee, there are different types of bleeding, and this study evaluated a

specific type of bleeding. So when we ask for your opinion and discussion around the indicated population, we're asking you to provide you a perspective on whether the risks are acceptable for all the subsets of the indicated population. Therefore, if there are certain subsets of the indicated population in which you think the risks are not acceptable or are acceptable, that will be an important point of discussion that we are very interested in. Thank you.

Dr. Koroshetz: That's very important. Thanks.

Dr. Ahsan: That clarifies things. So can I ask a question? And I guess maybe I'm misunderstanding a little bit, and this is to you, Dr. Fashoyin-Aje of the FDA, which is if we're looking at all life-threatening or uncontrolled bleeding, the metrics of looking at MRS, is that not inherently associated with ICH?

Dr. Fashoyin-Aje: Yes, so those metrics are associated with the population that was studied in the trial that is submitted for us to verify the clinical benefit for this indication. So I think you're right to point out that neurologic function may not be relevant to a patient who had a bleed in the hip or I don't know, somewhere else that is also serious and life-threatening. That's an appropriate distinction to make, and we're not at all suggesting that neurologic function may be applicable to the entire indicated population. So we welcome your thoughts on that. Thank you.

Dr. Ahsan: Yeah, so I guess that that's where I get a little challenged, and maybe I'm missing something and the other committee members see it more clearly. But in inherent to question number one is should we add neurological status to be incorporated in the assessment of benefit? But that benefit is only for a subpopulation of the indicated population, but yet in question two, we're asked about the risk. And so, it kind of positions us in a inconsistent manner to be talking about ICH and the outcomes related to those patients with ICH, yet the discussion is about the

applicability and the risk to the entire indicated population, which is much broader than that. And so I don't know if Dr. Fashoyin-Aje, if you had any more comment about that.

Dr. Fashoyin-Aje: No, I think you're right. I think we're speaking in the question number one, we're speaking specifically, because I think one has to consider the challenges of designing a study that evaluates patients with all types of bleeding. That is not a feasible study to design here. And so one study in a specific population was designed to evaluate the surrogate endpoint and also to evaluate this population with the intracranial bleeds. And the question number one is specifically speaking to the endpoints that the sponsor is proposing the no clinical benefit.

The second question is speaking to the risk of thromboses in the entire population that will receive this product. And so we understand what is challenging and what appears to be sort of discordant or two questions that may not be in alignment, but they're really distinct. So the first is really speaking to the specific population in ANEXXA-I. And the second is really speaking to the risks that we see in ANEXXA-I, the context of the entire indicated population. I don't know if that clarifies.

Dr. Ahsan: No, I mean, I think it's clear. I think that, you know, so you've asked two very separate questions, but I would just caution the committee when looking at your assessment of risk, then that MRS, that you not overweight MRS, which is for one subpopulation, when discussing the acceptable risks for the entire indicated population. Is there a clinician who'd like to challenge me on that or discuss what I just said in terms of whether or not I have that right or not or anyone else on the committee?

Dr. Ratan: I had a question. And I think the question is, who chose the indication to be studied? Was it chosen by the FDA or by the sponsor?

Dr. Ahsan: I'll let the FDA answer that. Should be a quick question, a quick answer. I think the sponsor is probably ready to answer. You can answer quickly.

Dr. Roe: Yes, if I can share a slide, please. We negotiated with the FDA. We chose the ICH population as part of the PMR requirements because you could verify hemostatic efficacy in a very precise way with brain imaging. You're not able to do that with GI bleeds or bleeds in other locations where you're unable to quantify the change in bleeding after the administration of treatment. And so this was part of the negotiations in 2018 on the PMR requirements to address the question.

Dr. Ahsan: Yeah, I mean, for sure. I think the ICH is more quantifiable. Thank you for that. Dr. Tifft?

Dr. Tifft: No, I was basically going to say the same thing. The way the study was designed, it was designed so that it would be easily available to be measured. And in fact, it is. And in fact, it showed a difference in that it did what it intended to do. The question is now the baggage, it seems to me, that came along with that was the population in which these things could be easily measured also happened to be 80 years old and have lots of comorbidities that may have sort of worked against the study if we're going to generalize it now to serious bleeds, life-threatening bleeds in other places aside from brains. So well understood that this was a population in which this intracranial hemorrhage could be easily measured, but the study population may not be reflective of the entire population that's going to be able to be benefiting from this drug.

Dr. Ahsan: Right. And once it's approved, then it's going to have much wider use. And so I think that this is where my, as a committee member, my comment is that, you know, we almost don't have the data to evaluate the serious risks or the only data that we can look at is mortality

because there is nothing else that is representative of the entire indicated population. Okay. That would be my, as a member, my comment. Okay. Dr. O'Brien.

Mr. O'Brien: Yes. Just to continue on that in terms of, it was very difficult in context. You know, I look at the data that was given to us, real world data and also the clinical data. For example, there's 70,000 patients that have taken this drug globally and there's 36,000 in the United States, but I don't have that stratified by type. I don't know whether or not they were GI bleeds or whether they're brain bleeds or other bleeds that occur. So I have no idea of what population in general is that is taking this particular drug. So again, it becomes very difficult to apply the very specific data that we've got for a very specific population in terms of a much larger population that is going to now take it. A personal, again, experience two months ago, I experienced a GI bleed being on Eliquis. Idiopathic GI bleed that bled significantly for a week. The treatment for that was to take me off the Eliquis and then do a colonoscopy. Now, thankfully, within a week, it resolved and it hasn't come back. I still don't know why it would have it, but it's there. So the question is, when you looked at the data again, 48, the sponsor told us that 48% of the bleeds is actually GI bleeds. Are we now going to have a vast amount of population of GI bleeds that are going to be given this drug? And what is the potential consequence? I have no way of knowing that in terms of voting. I have no way of noting that looking at this data other than to be concerned.

Dr. Ahsan: Exactly, exactly. I mean, with the over-focus on ICH, how does the GI bleed population fare in terms of the data that was presented? Dr. Snyder, I saw that your hand was up and it's no longer, if you still have a question, I'm happy to recognize you.

Dr. Snyder: Okay, can you hear me okay?

Dr. Ahsan: We can.

Dr. Snyder: Yeah, hi. I guess I'm going to echo some of the points that Dr. Tiff brought up and Dr. O'Brien brought up. As a clinician, this is a real conundrum. I really appreciate the passion of the ER docs when you're confronted with a patient who's bleeding. And as an intensivist, I know the first thing you want to do is simply just stop the bleeding. And later on, you can deal with the downstream consequences. But to get to what Dr. Tifft was saying, I'm wondering whether the indications can be more nuanced. There are many patients that are on DOACs who have never had a stroke, who have never had any kind of thrombotic event. They're on the DOACs to prevent it.

And then, of course, there are patients that are at very high risk for thrombotic events because they've had them in the past. They've had strokes, they've had MIs. And I'm just wondering whether, and the sponsor kind of alluded to this a little bit, that maybe when a clinician has this drug in its toolbox, they would know that a patient at high risk for a thrombotic event should not be given this drug.

Whereas those who are on DOACs for another indication would be the ones that would benefit from this drug. And that we can be more nuanced with the indications for this drug once it's in the toolbox, like we do with so many drugs.

Dr. Ahsan: Yeah, I think that's a great way to summarize it, is that it was a missed opportunity to understand the data at a deeper level so that we could parse out populations that benefit the most from this drug, as opposed to bundling it all into one indication, one analysis, et cetera. And that's unfortunate because it makes it difficult for us to look at the risk factors in a more elegant way than just with a blunt tool, as was provided. So I think that that's maybe how we can bring it

back to this question, which is it's hard to give a single monolithic answer to risk in this very diverse indicated population. Is that fair to say?

Dr. Snyder: Yeah, that's exactly the point, because it looks like the adverse outcomes mostly were related to thrombotic events, and they typically happened in patients that already had a history of thrombotic events that you may not want to use this drug on.

Dr. Ahsan: Right. To do over again, I think that we would change some of the clinical trial design, but that's not for us to really propose at this point. Okay, so are there any more comments before I try to summarize the comments that were made? Okay, great.

So I think we had some very good discussion, and I really appreciate the diversity of thinking and expertise on this committee and how they all contributed. I think when we think about question one, and we think about the efficacy endpoints, we're challenged, and question two, when we think about the risk, we're challenged by a few aspects, which is, this is a drug that is used in an acute way, but yet do we want to look at long-term effects? And it is very nuanced and a complex landscape. And as was mentioned by one of the clinicians, there are a lot of comorbidities in this population, and many of them are stroke prone. But then we saw a stratification of the data that indicated that depending on subpopulations within the overall indicated population, that there might be different levels of risk. I think the thing that is most confounding about the data is that we do see a decrease in hematoma volume change. We do see a dramatic decrease in anti-factor Xa reduction. But what we don't see is that connected to a clear clinical outcome that we can point to as a benefit. And meanwhile, we do see an increase in occurrence in the TEs and the mortality, so a negative effect on the mortality. So I guess that raises two questions, which is in the context of the goal, is the goal just an immediate reversal of the anticoagulation drug, or is it about a long-term impact? And as I think Dr. O'Brien said very

elegant, it's almost a question of definition. Are we trying to just stop the bleeding, or are we trying to look at long-term neurological outcome? And that is what makes question one very challenging about which assessments to add or to view as part of clinical benefit. And then when we look at question two about risk, as I mentioned, one of it was about the large number of comorbidities in this population. Another thing that was raised was dose and whether dosing has an impact and whether there's an opportunity for, is dose part of the equation when it comes to risk? And then I think ultimately what was also raised as a problem is that the question two was posed as a single question of serious risk for the indicated population, yet the discussion in the data was very much geared towards ICH.

And it's hard to view the overall risk for that entire indicated population on the data really geared towards a subset. So that's the challenge there in terms of giving a definitive clear answer on whether the risks are acceptable in the indicated population in the context of clinical efficacy.

I think that generally hits the big buckets of what we discussed. Before I turn it back over to FDA, was there something in the summary that I missed that someone thought that I should have reiterated? Okay.

Dr. Roe: Very good.

Dr. Ahsan: As we can move on. So at this point, I do want to return, I want to thank the committee. This was a great conversation. I think it hopefully will be of value to the FDA who is really looking for insight and comment on these questions. And I think that we did discuss many different elements that hopefully are a benefit to them. And so at this point, I'm going to turn it over to Dr. Verdun to close out the session. All right.

Dr. Fayoshin-Aje: Thank you, Dr. Ahsan. I'm going to close the session on behalf of the FDA. I want to thank the committee for a really robust discussion today. I want to thank the public commenters on the application. Thank the sponsor, the applicant for participating in today's meeting. And most importantly, we want to thank the patients who participated in this clinical trial and in many other clinical trials. This conversation was really very helpful to us. The discussion and the recognition of the complexities and the nuances of this. So we really, really appreciated hearing your thoughts on the various aspects of this application. So again, we just want to thank you on behalf of the agency for this meeting. And thank you, Dr. Ahsan, for keeping us all on track here today.

Closing Remarks/Adjournment

Dr. Reese: And I'd like to also say thank you for those wonderful closing remarks and for the work of the committee.

In closing, I want to thank everyone for all of their hard work and efforts, especially the committee members, our chairperson, Dr. Ahsan, CBER staff, and AV staff for working so hard to make this meeting a successful one. I now call this meeting officially adjourned at 3.56 p.m. Thank you.