sanofi

Review and Q&A Checkpoints:

Checkpoint 2

- *Hemophilia Competitor Grid*
- *ELOCTATE® & ALPROLIX® Clinical Compendium*

Facilitator Guide

MAT-US-2208072-v1.0-11/2022

Introduction

This Facilitator Guide is designed to help you follow a process that will ensure representatives under your leadership are well-prepared with the foundational knowledge that is critical to their careers at Sanofi.

Why Checkpoints?

As a facilitator, you have an opportunity to share your hard-earned experience in a meaningful way: through guidance and coaching. Through these series of Checkpoints, you will give learners opportunities to:

- Ask questions
- Review key content
- Verbalize complex concepts
- Prepare for success in the field

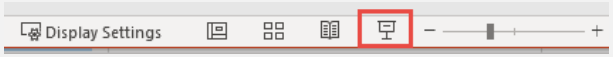
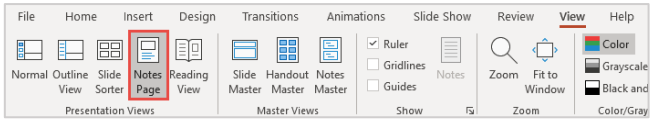
> “Leadership is about making others better as a result of your presence and making sure that impact lasts in your absence.”
>
> Sheryl Sandberg

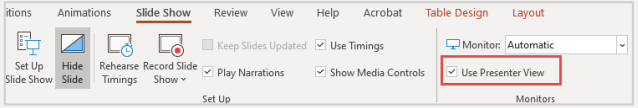
A great coach:

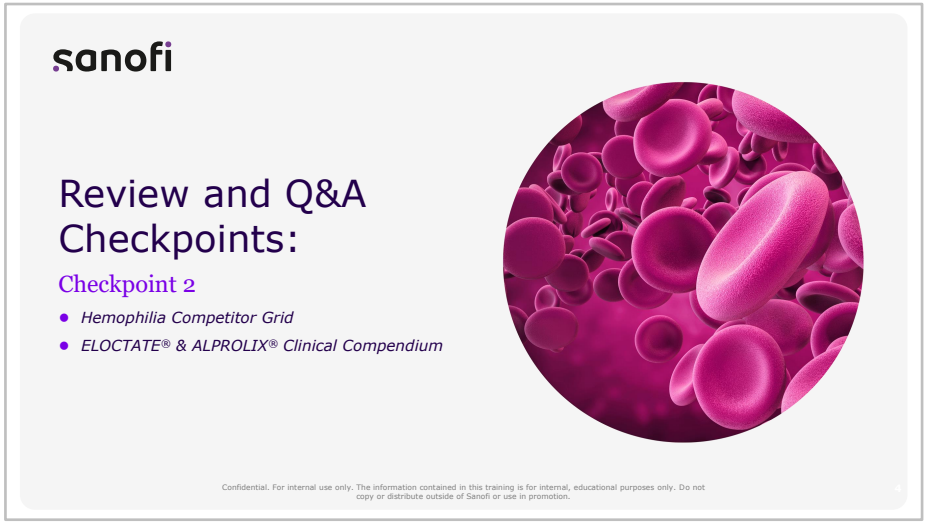
- Listens more than speaks
- Asks great questions
- Clarifies when needed
- Avoids “telling”
- Doesn’t judge
- Helps others commit to specific actions

How to Use This Guide

This workshop is developed in PowerPoint (PPT) to function as both a Facilitator Guide and presentation slides. Prior to the workshop, review this page to familiarize yourself with how to navigate the PPT seamlessly during the session.

View	Primary Audience	Primary Audience Sees	How to Access This View
Slideshow	Participants	• Full-screen slides • Share this view with participants on the big screen (in person) or on screenshare (virtual)	• Click the **slideshow icon** in the *Display Settings* on the right side of the bottom bar  • OR, click **Slide Show** on the top menu bar and select **From the Beginning** or **From Current Slide**
Facilitation Notes	Facilitator(s)	• Slide thumbnail • Facilitator directions for that slide	• Click **View** on the top menu bar • Select **Notes Page** (not Notes Master)  *Note: This same view appears in your PDF Facilitator Guide for printing and mark-up prior to the workshop.*

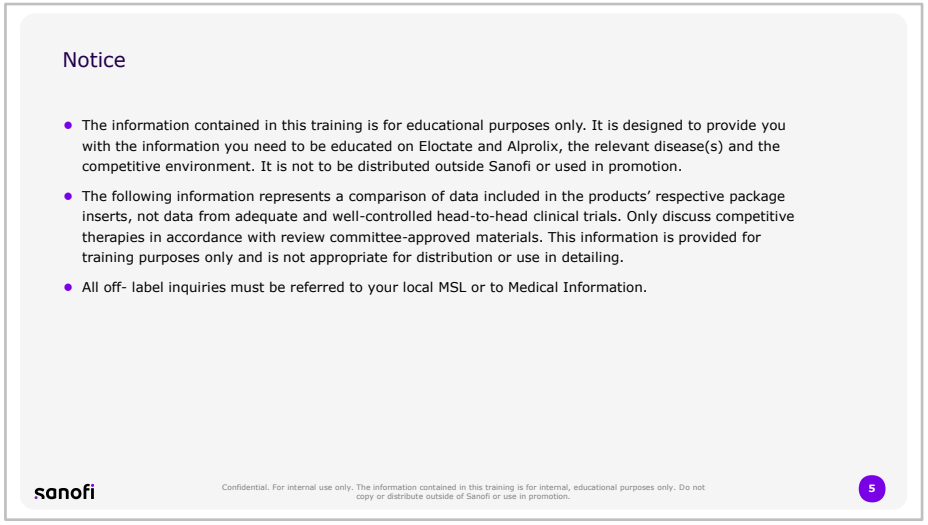
Presenter View (with multiple screens)	Facilitator(s)	**On presenting screen:**
		• Full-screen slides for participants to view
		
		On 2nd screen:
		• On left:
		  • Current slide
		• On right:
		  • Next slide thumbnail
		  • Facilitator directions for current slide (under next slide thumbnail)
			• Click **Slide Show** on the top menu bar
			• Click to select **Use Presenter View** checkbox if you would like it to show on a different screen while the audience views your projecting/shared screen
			 
			*Note: Hidden slides (eg, Workshop At-A-Glance on the previous page) will not show in Presenter View, so make sure to print those pages prior to facilitating. To determine hidden slides, click **View** on the top menu bar and select **Normal**. Hidden slides are dimmed in color and the slide number is crossed off.*



Key Concepts

- **Display** this slide on-screen as participants arrive.
- **Welcome** participants to *Checkpoint 2*.
- **Introduce** yourself and any other facilitators.

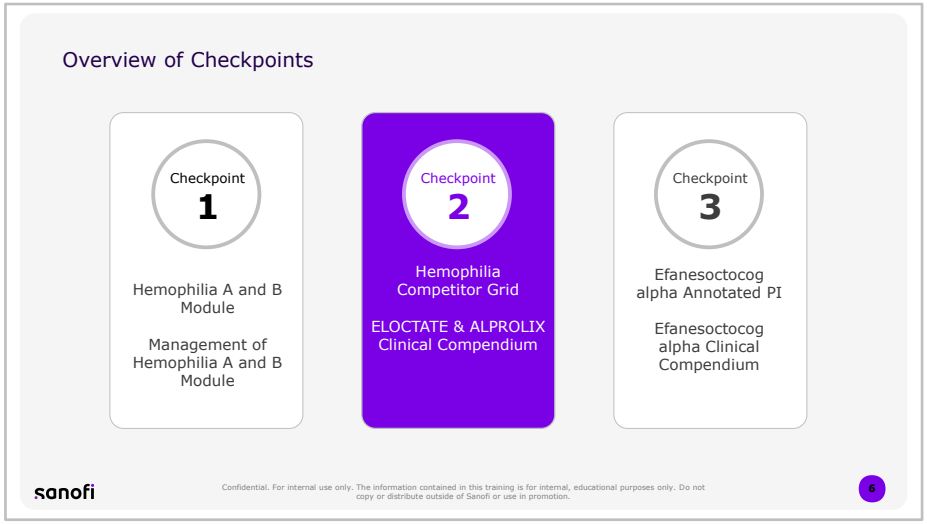
Facilitator Notes



Key Concepts

- **Review** on-screen content.

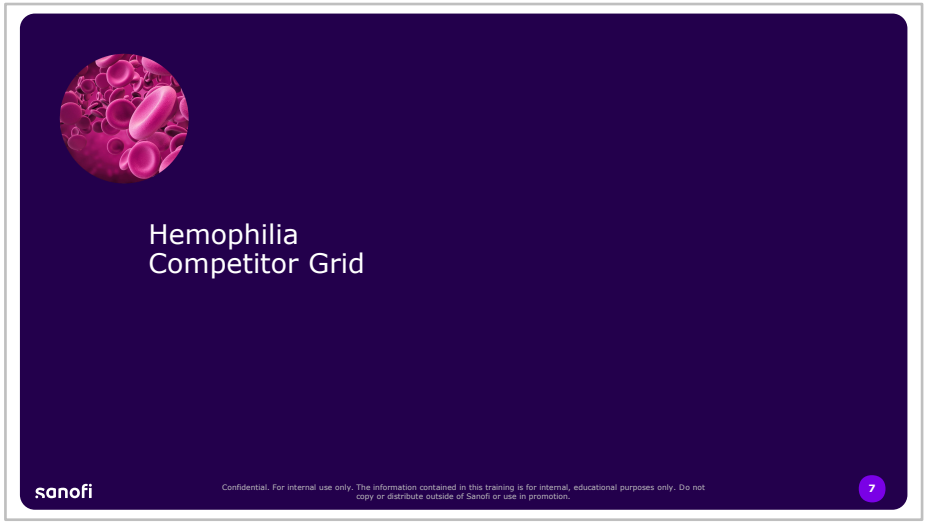
Facilitator Notes



Facilitator Notes

Key Concepts

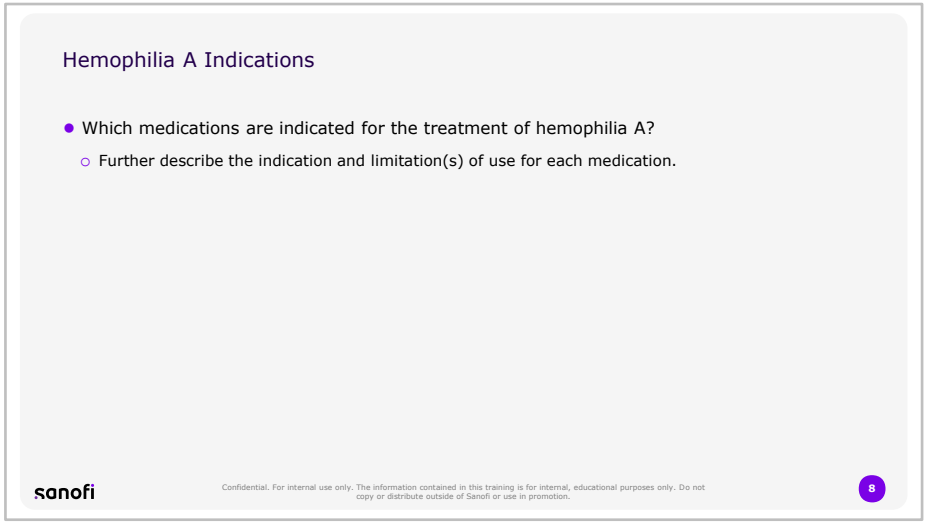
- **Provide** an overview of the three checkpoints that will be held during foundational training:
- **Say**: *Checkpoints are structured group sessions designed to provide you with an opportunity to review complex content. With my coaching and guidance at each session, you will:*
  - *Review applicable content*
  - *Ask questions in a safe environment*
  - *Practice verbalizing key concepts and information from the content you have studied at home*
  - *Get feedback on your verbalization skills*
- Checkpoints will cover the material from the deliverables seen on screen.
  - **Review** each checkpoint and its corresponding topic.



Key Concepts

Introduce the first deliverable for review during Checkpoint 2, the Hemophilia Competitor Grid.

Facilitator Notes



Facilitator Notes

Key Concepts

Adynovate®, **Afstyla®**, **Kovaltry®**: Indicated (Kovaltry: "for use") in children and adults with hemophilia A (congenital factor VIII deficiency) for:
- On-demand treatment and control of bleeding episodes
- Perioperative management (Afstyla and Kovaltry: "of bleeding")
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitation of use: Adynovate, Afstyla, and Kovaltry are not indicated for the treatment of von Willebrand disease

ELOCTATE, Esperoct®, Nuwiq®: Indicated (Esperoct: "for use") in adults and children with hemophilia A for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitation of use: ELOCTATE, Esperoct, and Nuwiq are not indicated for the treatment of von Willebrand disease

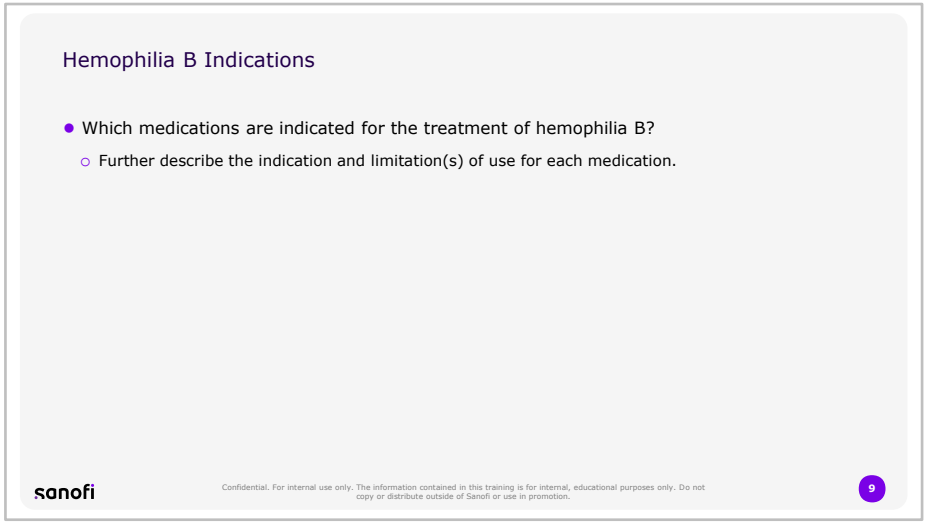
Jivi®: Indicated for use in previously treated adults and adolescents (≥12 years of age) with hemophilia A (congenital Factor VIII deficiency) for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitations of use
- Jivi is not indicated for use in children <12 years of age due to greater risk for hypersensitivity reactions
- Jivi is not indicated for use in previously untreated patients (PUPs)
- Jivi is not indicated for the treatment of von Willebrand disease

Advate®: Indicated for use in children and adults with hemophilia A (congenital factor VIII deficiency) for:
- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

Advate is not indicated for the treatment of von Willebrand disease

Hemlibra®: Indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors



Facilitator Notes

Key Concepts

ALPROLIX, Idelvion®: Indicated in adults and children with hemophilia B (congenital Factor IX deficiency) for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitation of use: ALPROLIX and Idelvion are not indicated for induction of immune tolerance in patients with hemophilia B

Rebinyn®: Indicated for use in adults and children with hemophilia B for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

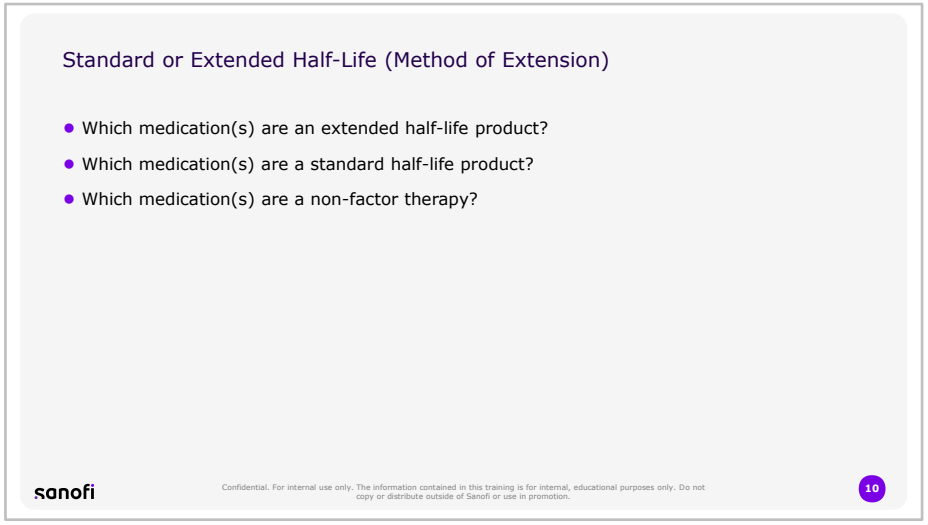
Limitations of use: Rebinyn is not indicated for immune tolerance induction in patients with hemophilia B

BeneFIX®: Indicated in adults and children with hemophilia B (congenital factor IX deficiency or Christmas disease) for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitation of use: BeneFIX is not indicated for induction of immune tolerance in patients with hemophilia B

Ixinity®: Indicated in adults and children ≥12 years of age with hemophilia B for:
- On-demand treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to reduce the frequency of bleeding episodes

Ixinity is not indicated for induction of immune tolerance in patients with hemophilia B



Facilitator Notes

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- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

Extended half-life product:

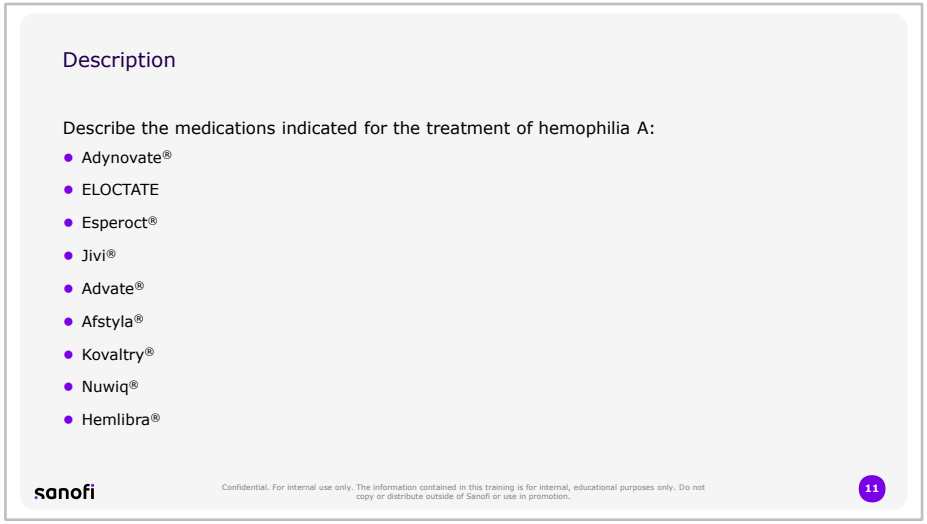
- Adynovate (PEGylation)
- ELOCTATE (Fc fusion)
- Esperoct (PEGylation)
- Jivi (PEGylation)
- ALPROLIX (Fc fusion)
- Idelvion (albumin fusion)
- Rebinyn (GlycoPEGylated)

Standard half-life product:

- Advate
- Afstyla
- Kovaltry
- Nuwiq
- BeneFIX
- Ixinity

Non-factor therapy:

- Hemlibra



Facilitator Notes

Key Concepts

- **Adynovate:** Adynovate is a PEGylated form of recombinant antihemophilic factor (Advate), which is produced by recombinant DNA technology from the Chinese hamster ovary (CHO) cell line
- **ELOCTATE:** B-domain deleted recombinant Factor VIII, Fc fusion protein is the active ingredient and is produced by recombinant DNA technology from a human embryonic kidney cell line
- **Esperoct:** Esperoct is a recombinant analogue of human coagulation Factor VIII (FVIII) conjugated with a 40-kDa polyethylene glycol (PEG) molecule. The FVIII protein in Esperoct is produced in CHO cells using recombinant DNA technology
- **Jivi:** Jivi is an antihemophilic factor (recombinant), PEGylated-aucl and is a recombinant DNA-derived, Factor VIII concentrate. Specifically, it is produced by site-specific conjugation of the active protein BDD-rFVIII produced by recombinant DNA technology in baby hamster kidney (BHK) cells and is conjugated at an amino acid within the A3 domain with a branched PEG moiety
- **Advate:** Purified glycoprotein recombinant antihemophilic factor synthesized by a genetically engineered CHO cell line but does not contain plasma or albumin; the CHO cell line employed in the production of Advate is derived from that used in the biosynthesis of Recombinate
- **Afstyla:** Single-chain recombinant Factor VIII produced in CHO cells. No human- or animal-derived proteins used in the purification or formulation processes
- **Kovaltry**: Recombinant, human DNA sequence-derived, full-length Factor VIII concentrate produced by a genetically engineered baby hamster kidney cell line into which the human Factor VIII gene was introduced together with the human heat shock protein (HSP) 70 gene; HSP 70 is an intracellular protein that improves proper folding of the Factor VIII protein
- **Nuwiq**: Active ingredient is B-domain-deleted recombinant Factor VIII (BDD-rFVIII), produced by recombinant DNA technology in genetically modified human embryonic kidney (HEK) cells with no animal- or human-derived materials added during the manufacturing process or to the final product
- **Hemlibra**: Emicizumab-kxwh is a humanized monoclonal modified IgG4 bispecific antibody binding factor IXa and factor X and is produced in genetically engineered CHO cells

Description

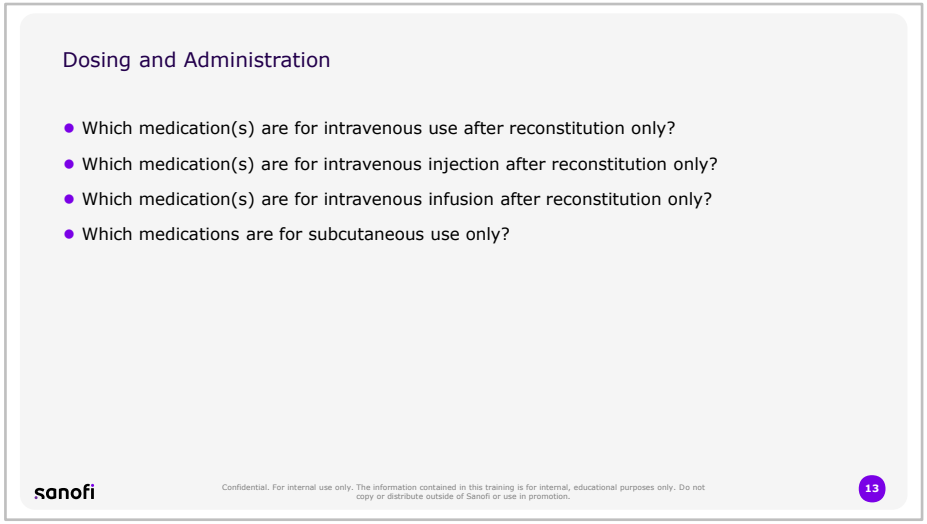
Describe the medications indicated for the treatment of hemophilia B:

- ALPROLIX
- Idelvion®
- Rebinyn®
- BeneFIX®
- Ixinity®

Facilitator Notes

Key Concepts

- **ALPROLIX:** Active ingredient is a recombinant coagulation Factor IX fusion protein consisting of the human coagulation Factor IX sequence covalently linked to the Fc domain of human immunoglobulin GI (IgG_1); it is not derived from human blood and the recombinant Factor IX Fc fusion protein is expressed in a HEK cell line
- **Idelvion:** Active ingredient is recombinant coagulation Factor IX albumin fusion protein, a purified protein produced by recombinant DNA technology. It is manufactured without the addition of proteins derived from human or animal source material. It is a glycoprotein secreted by a genetically engineered CHO cell line
- **Rebinyn:** Purified recombinant human Factor IX with a 40 kiltodaltons (kDa) PEG conjugated to the protein; produced by recombinant DNA technology in CHO cells
- **BeneFIX:** Purified protein produced by recombinant DNA technology produced by a genetically engineered CHO cell line
- **Ixinity:** Coagulation factor IX (recombinant) is a purified protein secreted by a genetically engineered mammalian cell line derived from CHO cells



Facilitator Notes

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Key Concepts

Intravenous use after reconstitution only:

- Adynovate
- Jivi
- Afstyla
- Kovaltry
- Nuwiq
  - Please note Nuwiq does not have the word "only" under Dosing and administration in the PI, however there is not another type of dosing listed
- ALPROLIX
- Idelvion
- Rebinyn
- BeneFIX
- Ixinity

Intravenous injection after reconstitution only:

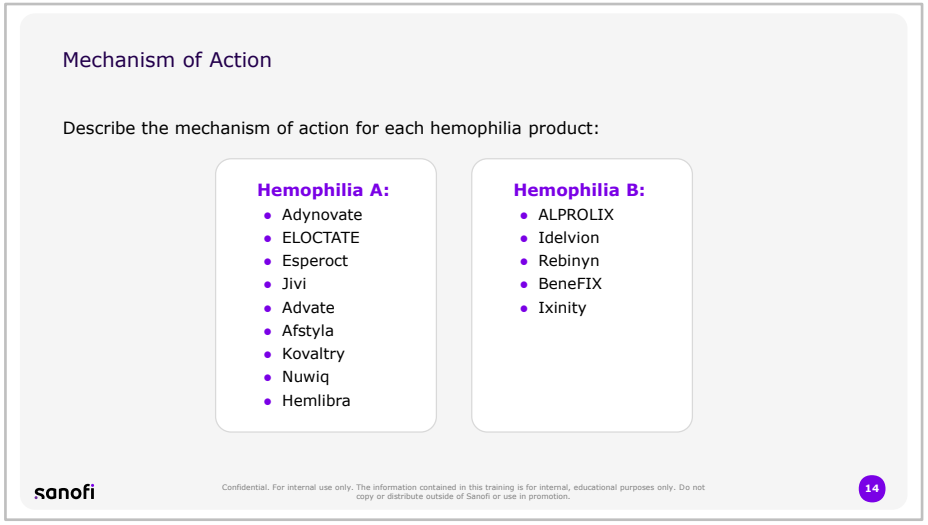
- ELOCTATE
- Advate

Intravenous infusion after reconstitution only:

- Esperoct

Subcutaneous use only:

- Hemlibra



Facilitator Notes

Key Concepts

Hemophilia A:

- **Adynovate, Esperoct:** Temporarily replaces the missing coagulation factor VIII needed for effective hemostasis in congenital hemophilia A patients
- **ELOCTATE, Advate:** Temporarily replaces the missing Coagulation Factor VIII needed for effective hemostasis
- **Jivi:** Temporarily replaces the missing coagulation Factor VIII
- **Afstyla:** Replaces the missing Coagulation Factor VIII needed for effective hemostasis
- **Kovaltry, Nuwiq:** Temporarily replaces the missing clotting Factor VIII that is needed for effective hemostasis
- **Hemlibra:** Bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis

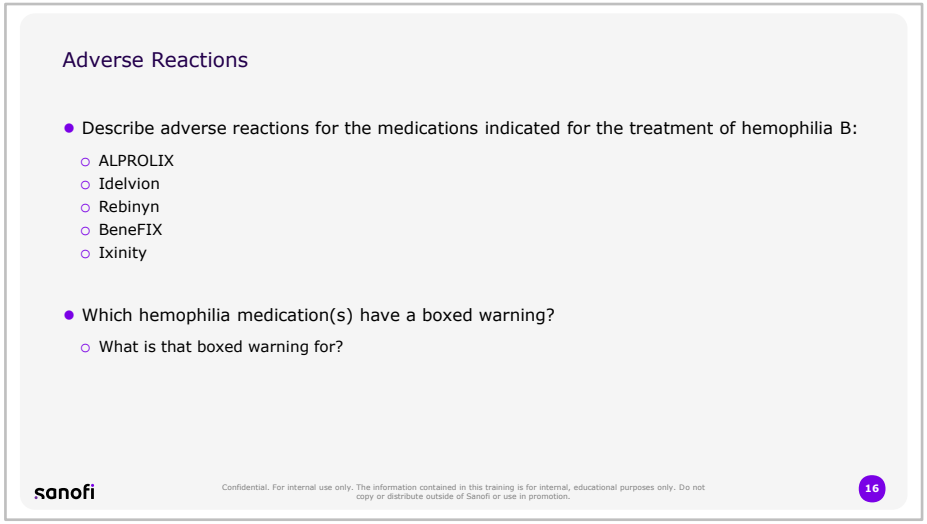
Hemophilia B:

- **ALPROLIX, Idelvion:** Temporarily replaces the missing coagulation Factor IX needed for effective hemostasis
- **Rebinyn:** Temporarily replaces the missing coagulation Factor IX
- **BeneFIX:** Temporarily replaces the missing clotting factor IX that is needed for effective hemostasis
- **Ixinity:** Replaces factor IX, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies

Facilitator Notes

Key Concepts

- **Adynovate:** Most common adverse reactions (≥1% of subjects) were headache, diarrhea, rash, nausea, dizziness, and urticaria
- **ELOCTATE:**
  - Previously treated patients (PTPs): Most frequently occurring adverse reactions (incidence >0.5% of subjects) were arthralgia, malaise, myalgia, headache, and rash
  - PUPs: Most frequently occurring adverse reactions (incidence ≥1.0% of subjects) were Factor VIII inhibition, device-related thrombosis, and rash papular
- **Esperoct:** Most frequently reported adverse reactions (incidence ≥1%) were rash, redness, itching (pruritus), and injection site reactions
- **Jivi:** Most frequently (≥5%) reported adverse reactions in PTPs ≥12 years of age were headache, cough, nausea, and fever
- **Advate:** Most common adverse reactions (frequency >5% of subjects) were pyrexia, headache, cough, nasopharyngitis, arthralgia, vomiting, upper respiratory tract infection, limb injury, nasal congestion, and diarrhea
- **Afstyla:** Most common adverse reactions (>0.5% of subjects) were dizziness and hypersensitivity
- **Kovaltry**: Most frequently reported adverse reactions (≥5%) were inhibitors in PUPs/minimally treated patients (MTPs), pyrexia, headache, and rash
- **Nuwiq**: Most common adverse reactions (>5% of subjects) were upper respiratory tract infection, headache, fever, cough, lower respiratory tract infection, rhinitis, chills, abdominal pain, arthralgia, anemia, and pharyngitis
- **Hemlibra**: Most frequently reported adverse reactions observed in ≥10% of patients treated were injection site reactions, headache, and arthralgia



Facilitator Notes

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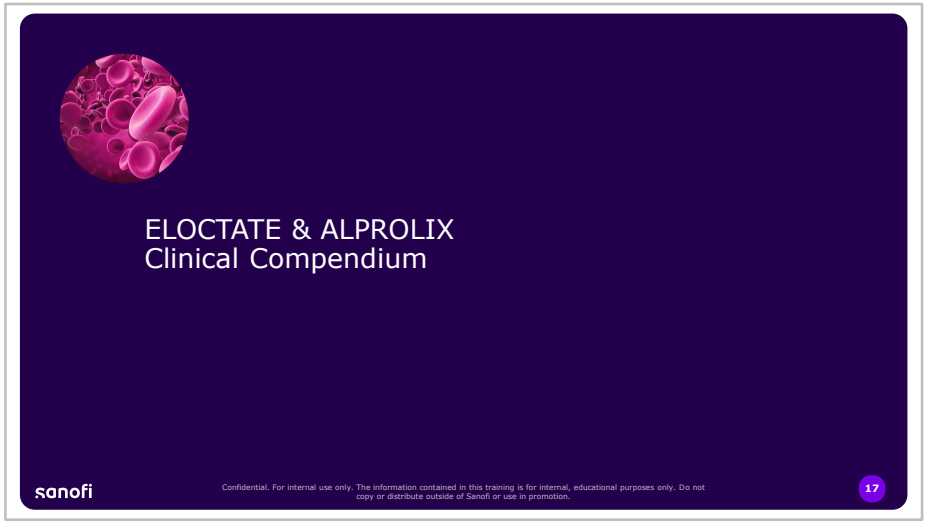
Key Concepts

Adverse reactions:

- **ALPROLIX:**
  - PUPs: Most common adverse reactions (incidence ≥1%) were injection site erythema, hypersensitivity, and Factor IX inhibition
  - PTPs: Most common adverse reactions (incidence ≥1%) were headache, oral paresthesia, and obstructive uropathy
- **Idelvion:** Most common adverse reactions (incidence ≥1%) reported were headache and dizziness
- **Rebinyn:** Common adverse reactions (incidence ≥1%) reported were itching and injection site reactions
- **BeneFIX:** Most common adverse reactions (frequency >5% of PTPs or PUPs) were fever, cough, headaches, dizziness, nausea, injections site reaction, injection site pain and skin-related hypersensitivity reactions (eg, rash, hives)
- **Ixinity:** Most common adverse reaction (>2%) was headache

Boxed warning:

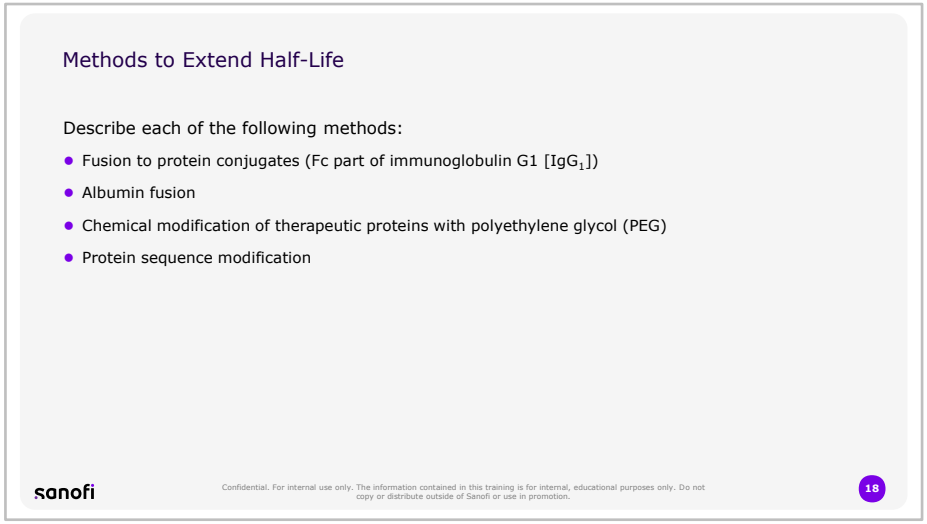
- **Hemlibra:** Thrombotic microangiopathy and thromboembolism



Key Concepts

Introduce the second deliverable for review during Checkpoint 2, the ELOCTATE and ALPROLIX Clinical Compendium.

Facilitator Notes



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Key Concepts

Fusion to protein conjugates (Fc part of IgG_1)

- The Fc domain of IgG_1 is engineered to form continuous polypeptides with clotting factors that remain longer in the plasma because they are cleared more slowly than the native factor and recycled back into circulation.
- Fusion of the Fc domain of IgG_1 to a therapeutic protein prolongs half-life through binding to the neonatal FC receptor (FcRn), which is expressed in endothelial cells lining the vasculature, protects both the endocytosed IgG_1 and Fc fusion proteins from lysosomal degradation and cycles them back into circulation.

Albumin fusion

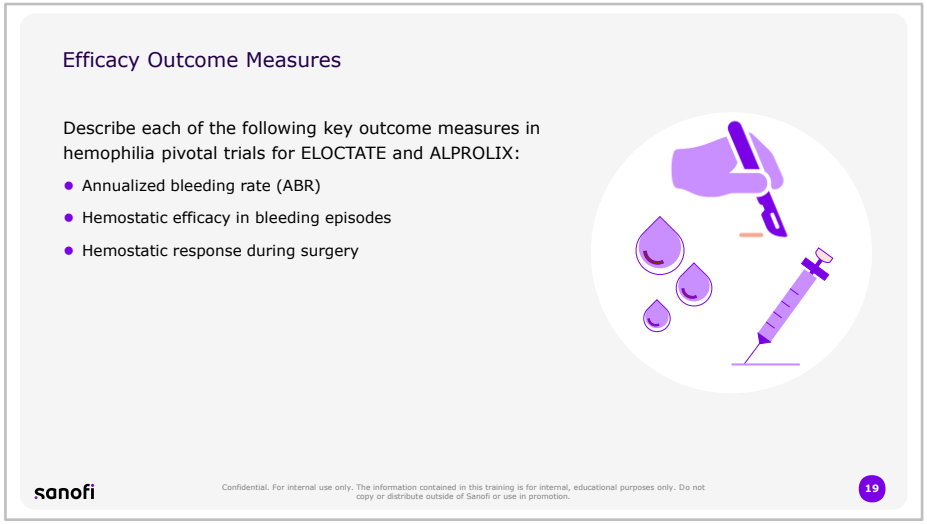
- Albumin is an inert carrier protein with a half-life of 20 days and is one of the most abundant plasma proteins.
- Recombinant FIX albumin fusion protein (rIX-FP) uses albumin fusion technology by joining recombinant human albumin to recombinant FIX (rFIX) by a cleavable linker.
- The cleavable linker is activated by Factor VIIa (FVIIa) or Factor XIa (FXIa) simultaneously releasing rFIX for hemostasis along with albumin; the albumin is then processed by the liver.
- rIX-FP has a half-life of 92 hours, which is nearly 5 times greater than the half-life of rFIX.

Chemical modification of therapeutic proteins with PEG

- Linking one or more PEG chains to a therapeutic molecule is known as PEGylation.
- The PEG molecule is non-immunogenic, non-toxic, and highly hydrophilic; PEG conjugation increases the circulation time of Factor VIII (FVIII) and Factor IX (FIX) mainly by protecting against enzymatic digestion and blocking interaction with clearance receptors.

Protein sequence modification

- Normally, human FVIII consists of 2 glycoprotein chains and circulates in plasma in a complex with von Willebrand factor (vWF); its light chain and heavy chain are held together by non-covalent interactions.
- A recombinant FVIII single chain has been developed; this single-chain preparation consists of a truncated B-domain that covalently links the heavy and light chains—the 3 predominant thrombin cleaving sites are not affected; activation by thrombin leads to a structurally normal activated FVIII molecule and markedly increased affinity to vWF and leads to prolonged half-life.



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Key Concepts

Annualized bleeding rate (ABR):

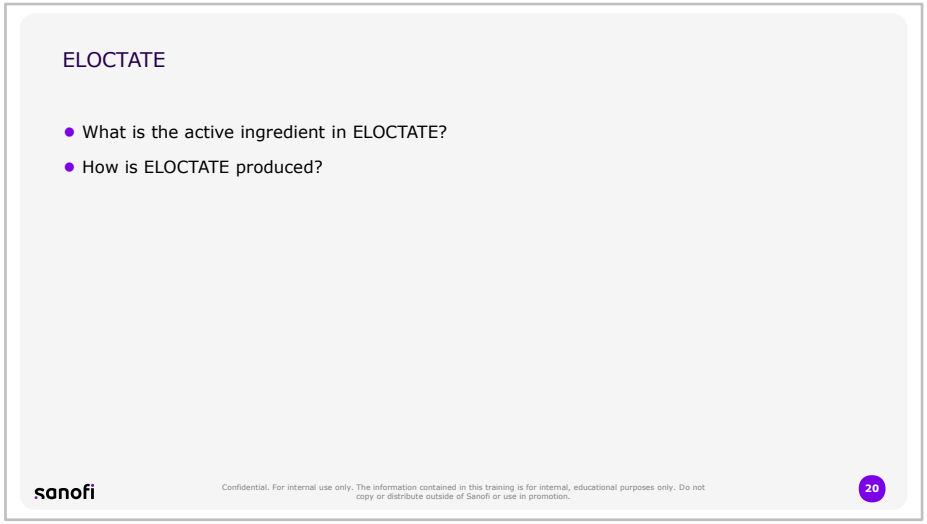
- The ABR is calculated as the number of reported bleeding events divided by the number of months in the reported time window and multiplied by 12.
- ABR estimation is prone to subjective assessment given that patients and treating physicians must define each bleed.

Hemostatic efficacy in bleeding episodes

- The number of injections and dose of injections required to resolve a bleeding episode is another outcome measure.
- This is an investigator-rated response.
- In addition, patients may report the response to each injection on a 4-point scale to include: Excellent, Good, Moderate, and No Response.

Hemostatic response during surgery

- Hemostatic response during surgery is assessed by an investigator using the scale of: Excellent, Good, Fair, Poor/None.



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Key Concepts

- B-domain deleted recombinant Factor VIII, Fc fusion protein (BDD-rFVIIIFc) is the active ingredient in ELOCTATE
- ELOCTATE is produced by recombinant DNA technology from a HEK cell line. The HEK cells assemble the amino acids to create Factor VIII. The original human cell line, from which the manufacturing cell lines were derived, was established in 1977 and continues to be used today to produce the factor for ELOCTATE
- ELOCTATE contains the Fc region of human IgG_1, which binds to FcRn.
- FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by cycling them back into circulation and prolonging their plasma half-life.

Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
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Key Concepts

A-LONG:

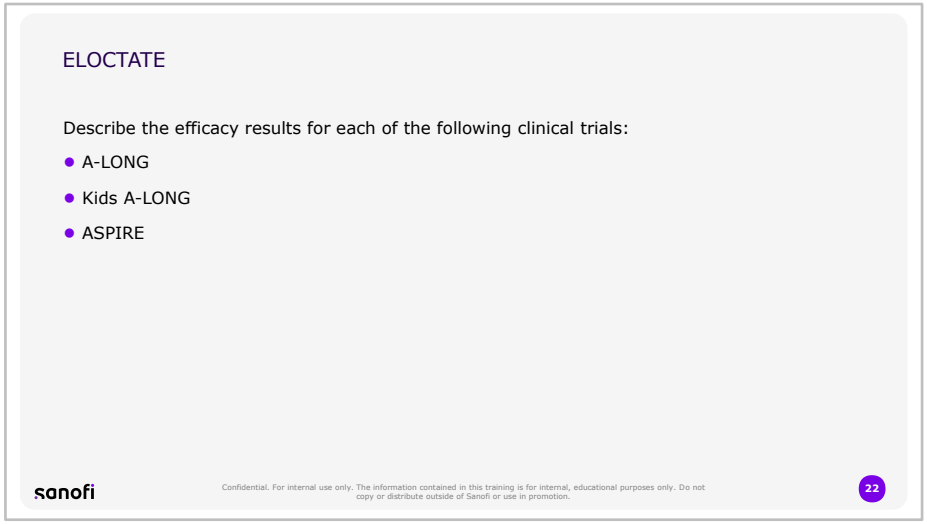
- Phase 3, open-label, multicenter, partially randomized study evaluating the comparative pharmacokinetics of recombinant Factor VIII fusion protein (rFVIIIFc) and recombinant Factor VIII (rFVIII) and the safety, tolerability, and efficacy of repeated rFVIIIFc dosing for prophylaxis, treatment of acute bleeding, and perioperative management in previously treated adolescents and adults with hemophilia A
- Inclusion criteria: Previously treated male patients aged ≥12 years old with severe hemophilia A (<1 International Unit [IU]/deciliter [dL] [1%] endogenous FVIII activity or severe genotype) if treated prophylactically or episodically with a history of ≥12 bleeding episodes in the 12 months prior to the study
- Exclusion criteria: History of inhibitors, history of hypersensitivity associated with any FVIII concentrate or intravenous (IV) immunoglobulin, or other coagulation disorders

Kids A-LONG:

- Phase 3, open-label, multicenter study of the safety, efficacy, and pharmacokinetics of rFVIIIFc in previously treated children aged <12 years with severe hemophilia A
- Inclusion criteria: Children aged <12 years with severe hemophilia A (endogenous FVIII activity of <1 IU dL-1 [<1%]) or a documented genotype known to produce severe hemophilia A; patients had to have been previously treated (received treatment with any recombinant or plasma-derived FVIII product for at least 50 exposure days [EDs] [defined as a 24-hour period during which replacement factor was administered one or more times])
- Exclusion criteria: Patients with a history of or currently detectable inhibitor (ie, neutralizing antibody activity at screening of ≥0.6 Bethesda unit (BU) milliliters (mL)-1 determined with the Nijmegen-modified Bethesda assay), history of anaphylaxis associated with any FVIII or IV immunoglobulin administration, or other coagulation disorders in addition to hemophilia A

ASPIRE:

- Eligible subjects completing A-LONG or Kids A-LONG could enroll in ASPIRE, a phase 3, open-label, non-randomized, global, long-term extension trial to assess the long-term safety and efficacy of rFVIIIFc for prevention and treatment of bleed episodes in previously treated adults and children with severe hemophilia A
- Inclusion criteria: Previously treated adults (≥150 documented EDs) and children (≥50 EDs) with severe hemophilia A (<1 IU/dL [<1%] endogenous FVIII activity); completed A-LONG or Kids A-LONG
- Exclusion criteria: Subjects with a history of anti-FVIII neutralizing antibodies (inhibitors), hypersensitivity associated with any FVIII concentrate or IV immunoglobulin, or other coagulation disorders



Facilitator Notes

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Key Concepts

A-LONG:

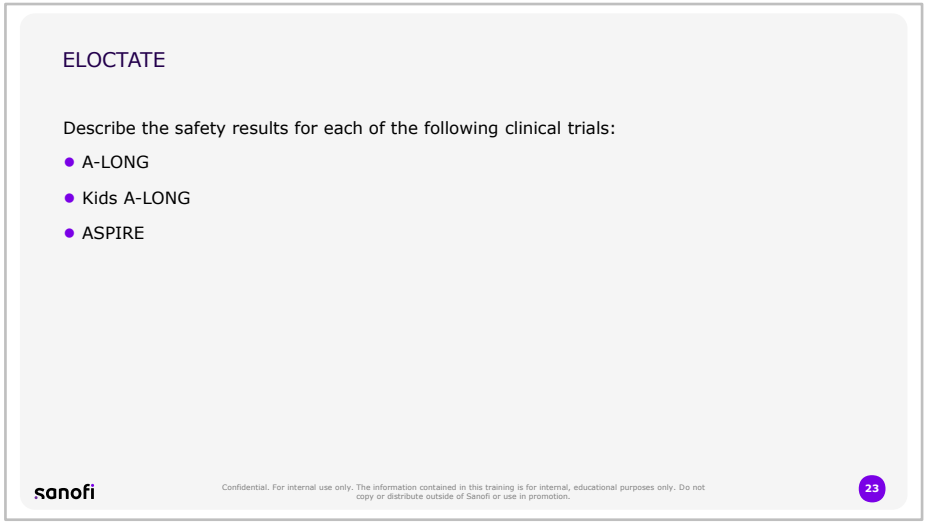
- The ABR was significantly reduced with prophylaxis in arm 1 (92%) compared with arm 3 (episodic treatment); 2.91 and 37.25 for arms 1 and 3, respectively; *P*<.001
- 87.3% of bleeding episodes were resolved with 1 injection
- There were 9 major surgeries performed in 9 subjects; the hemostatic response during the perioperative period for these surgers was rated by the investigators as excellent (n=8) or good (n=1)

Kids A-LONG:

- Overall, 46.4% of subjects in the study reported no bleeding events
- A total of 86 bleeding episodes occurred in 37 subjects, and a single infusion was sufficient to resolve the majority (81.4%) of bleeding episodes; 93% were resolved with 1 or 2 infusions
- There were no major surgical procedures performed with rFVIIIFc on study; in 7 minor surgical procedures in 7 subjects, the hemostatic response was evaluated by the investigator as excellent (n = 5) or good (n = 2)

ASPIRE:

- Median overall ABRs during ASPIRE for subjects from A-LONG were:
  - Individualized prophylaxis (IP): 0.7
  - Weekly prophylaxis (WP): 2.2
  - Modified prophylaxis (MP): 5.0
  - Episodic treatment (ET): 16.1
- Overall ABR during ASPIRE for subjects from Kids A-LONG were:
  - IP: 1.1
  - MP: 4.1
- >75% of acute bleed episodes were controlled by one rFVIIIFc infusion
- Of the 37 major surgeries, 33 were assessed for hemostatic response and all were rated as excellent or good



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Key Concepts

A-LONG:

- No inhibitors were detected in any subjects with an evaluable inhibitor test, including 110 subjects with ≥50 EDs, for whom the inhibitor incidence was 0%; the inhibitor incidence overall was also 0%
- The types of adverse events (AEs) were representative of events occurring in the general hemophilia population; the most common (incidence of ≥5% in the combined arms, excluding the perioperative period) were:
  - Nasophyngitis
  - Arthralgia
  - Headache
  - Upper respiratory infection

Kids A-LONG:

- No subjects developed an inhibitor to rFVIIIFc; the estimated inhibitor incidence rate was 0.00% overall, and 0.00% among 61 subjects with at least 50 rFVIIIFc EDs
- Of the 69 pediatric subjects treated with rFVIIIFc, 59 (85.5%) reported at least one AE on study, giving a total of 213 AEs
- Summary of AEs (≥3% in the total population) include:
  - Cough, upper respiratory tract infection, fall, nasopharyngitis, upper abdominal pain, head injury, headache, vomiting, diarrhea, ear infection, fatigue, pain in extremity, pharyngitis, seasonal allergy, tonsillitis, arthralgia, joint swelling, pyrexia, rhinorrhea, viral upper respiratory tract infection

ASPIRE:

- No subject developed an inhibitor during ASPIRE, and rFVIIIFc was well tolerated, with an AE pattern consistent with those expected for subjects with severe hemophilia A
- Most common AEs (≥10% per parent study population) include:
  - Nasopharyngitis
  - Upper respiratory tract infection
  - Fall
  - Arthralgia
  - Headache
  - Diarrhea
  - Cough
  - Hemophilic arthropathy
  - Vomiting
  - Seasonal allergy
  - Tonsillitis

Facilitator Notes

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Key Concepts

PUPs A-LONG:

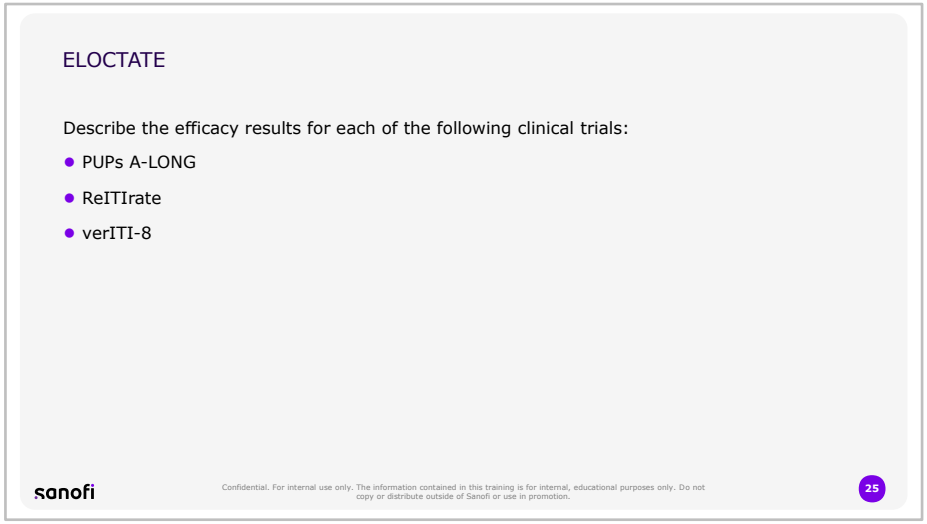
- Open-label, multicenter, phase 3 study that enrolled male pediatric PUPs with severe hemophilia A to receive rFVIIIFc
- Inclusion criteria: Males <6 years of age with severe hemophilia A defined as <1 IU/dL (<1%) endogenous FVIII, with no prior exposure to blood components or infusion with a FVIII concentrate (including plasma-derived and rFVIII)
- Exclusion criteria:
  - History of positive inhibitor testing
  - Infusion with commercially available rFVIIIFc at any time before screening
  - Other coagulation disorder(s)
  - Any concurrent clinically significant major disease

ReITIrate: a prospective, interventional, multicenter, open-label phase 4 study to evaluate rescue immune tolerance induction (ITI) with rFVIIIFc in patients who had experienced previous ITI failures

- 16 patients who had multiple risk factors for poor ITI outcome and long duration of previous ITI were enrolled
- Primary endpoint was ITI success within 60 weeks, defined as achieving all of the following:
  - Negative inhibitor titre (<0.6 BU/mL by the Nijmegen-modified Bethesda assay) at two consecutive visits;
  - FVIII incremental recovery (IR) >66% of the expected IR at 2 consecutive visits;
  - FVIII terminal half-life ≥7 hours

verITI-8:

- First prospective study of rFVIIIFc in first-time ITI; continues from the reITIrate study of rFVIIIFc for rescue ITI
- Prospective, single-arm, open-label, multicenter phase 4 study exploring the efficacy of rFVIIIFc for first-time ITI in people with severe hemophilia A with high titer-inhibitors (historical peak ≥5 BU/mL)
- Initial screening followed by ITI period in which subjects received rFVIIIFc 200 IU/kg/day until tolerization or 48 weeks had elapsed
- 16 subjects were enrolled and received ≥1 rFVIIIFc dose
- The primary endpoint was time to tolerization (successful ITI) with rFVIIIFc defined by inhibitor titer <0.6 BU/mL, incremental recovery (IR) ≥66% of expected IR (IR ≥1.32 IU/dL per IU/kg) (both at 2 consecutive visits), and half-life ≥7 hours within 48 weeks



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Key Concepts

PUPS A-LONG:

- The median overall ABR while on any prophylaxis regimen was 1.49
- 72% of the bleeds in the OD group and 80% of the bleeds in the prophylaxis group were resolved with 1 infusion
- 89% of the bleeds in the OD group and 94% of the bleeds in the prophylaxis group required ≤2 infusions for resolution
- The median total dose of rFVIIIFc required to resolve bleeding episodes was 54.5 IU/kg per bleeding episode in the OD group and 55.6 IU/kg per bleeding episode in the prophylactic group

ReITIrate:

- 7 patients withdrew prematurely
- Of the 9 completing the ITI period:
  - 4 reached confirmed negative inhibitor titer (<0.6 BU/mL) within 19 (11-60) weeks (median [range]), and 3 of these also reached incremental recovery >66% of expected, 2 of which reached a half-life ≥7 hours
- ITI success (meeting all criteria with no relapse) was achieved by 1 patient after 46 weeks. Partial success at final outcome was registered for 2 patients after 56 weeks and 30 weeks, respectively

verITI-8:

- 12 (75%), 11 (69%), and 10 (63%) subjects, respectively, achieved a negative inhibitor titer, an IR >66%, and a half-life ≥7 hours within 48 weeks

Facilitator Notes

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Key Concepts

PUPS A-LONG:

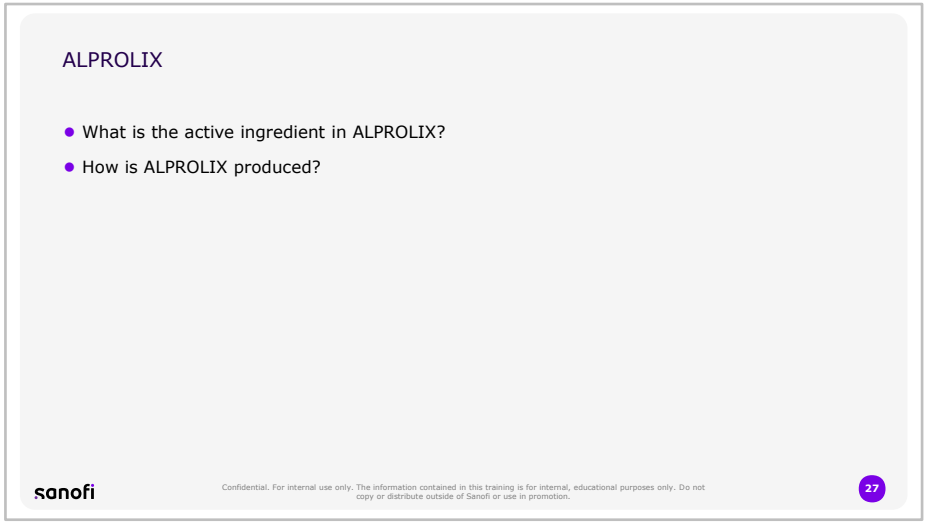
- The overall incidence of inhibitor development was 31.1%
  - At the time of inhibitor development, 7 subjects were receiving rFVIIIFc OD and 21 were receiving prophylaxis
- Nasopharyngitis was the most common AE in the group receiving the OD regimen and upper respiratory tract infection was the most common AE in the prophylaxis group

ReITIrate:

- 188 treatment-emergent adverse events (TEAEs) were reported in all 16 patients; 2 of the serious TEAEs (brachiocephalic vein thrombosis and vena cava thrombosis) occurred in the same patient and were considered related to ITI treatment by the investigator
- No new safety concerns were identified during the study, despite the intense ITI treatment
- Flow cytometry immunophenotyping indicated an increase in regulatory T cells
- Anti-drug antibody titer decreased in 11 patients
- IgG subclasses and epitope targeting were also characterized

verITI-8:

- All 16 subjects experienced ≥1 TEAE, the most frequent of which was pyrexia in 7 subjects; 1 subject reported ≥1 related TEAE (injection site pain)
- 9 subjects experienced ≥1 treatment-emergent serious AE (TESAE); TESAEs occurring in ≥2 subjects included vascular device infection, contusion, and hemarthrosis
- No treatment-related TESAEs, discontinuations due to AEs, or deaths were reported



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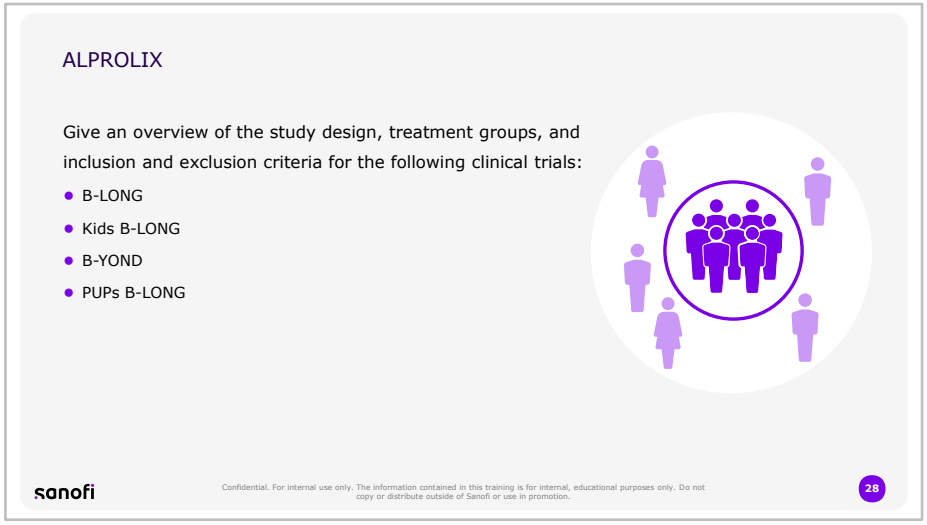
Key Concepts

- Coagulation Factor IX (recombinant), Fc Fusion Protein (rFIXFc), is the active ingredient in ALPROLIX and is a recombinant coagulation Factor IX fusion protein consisting of the human coagulation Factor IX sequence covalently linked to the Fc domain of human immunoglobulin (IgG_1)
- ALPROLIX is a recombinant Factor IX Fc fusion protein and is expressed in a HEK cell line. The HEK cells assemble the amino acids to create factor IX. The original human cell line, from which the manufacturing cell lines were derived, was established in 1977 and continues to be used today to produce ALPROLIX
- ALPROLIX contains the Fc region of human IgG_1, which binds to the FcRn. FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by cycling them back into circulation and prolonging their plasma half-life.



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Key Concepts

B-LONG: Phase 3, non-randomized, open-label, multicenter study to compare the pharmacokinetics of rFIXFc with those of recombinant factor IX and to assess the safety and efficacy of repeated administration of rFIXFc for the prevention and treatment of bleeding in adolescents and adults with severe hemophilia B

- 123 patients enrolled into 1 of 4 groups
- Inclusion criteria: Male patients 12 years of age or older with severe hemophilia B (≤2 IU of endogenous factor IX/dL) who were receiving prophylaxis or had a history of at least 8 bleeding events in the year before enrollment and had been previously treated with at least 100 injections of replacement factor IX (ie, had accrued at least 100 EDs)
- Exclusion criteria:
  - History of development of inhibitors (ie, neutralizing antibodies) or anaphylaxis associated with factor IX or IV immunoglobulin
  - Other coagulation disorders, uncontrolled infection with human immunodeficiency virus (HIV), renal dysfunction, or active hepatic disease

Kids B-LONG: Multicenter, open-label, phase 3 study assessing the safety, efficacy, and pharmacokinetics of rFIXFc in previously treated children with hemophilia B <12 years of age

- Inclusion criteria: Patients eligible for Kids B-LONG were boys <12 years of age with hemophilia B (≤2 IU/dL [≤2%] endogenous FIX activity) or a documented genotype known to cause severe hemophilia B who were previously treated with any recombinant or plasma-derived FIX product for 50 or more EDs with no history of or currently active inhibitors
- Exclusion criteria:
  - Other coagulation disorder(s) in addition to hemophilia B
  - History of anaphylaxis associated with any FIX or IV immunoglobulin administration
  - Active renal or hepatic disease
  - Any concurrent clinically significant major disease that, in the opinion of the investigator, would have made the subject unsuitable for enrollment
  - Current systemic treatment with chemotherapy and/or other immunosuppressant drugs, with the following exceptions: use of steroids for treatment of asthma or management of acute allergic episodes, and routine immunizations
  - Participation within the past 30 days in any other clinical study involving investigational drugs
  - Surgery within 30 days prior to the screening visit

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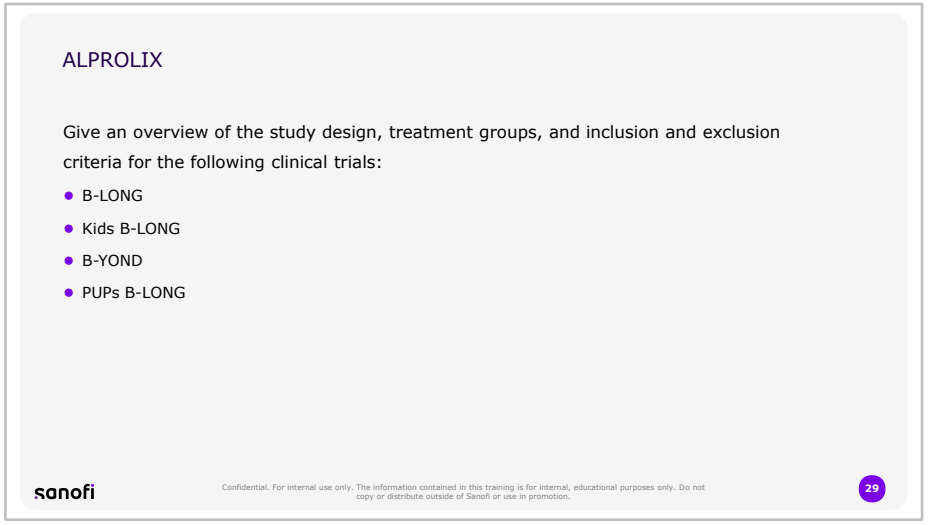

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Key Concepts

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B-YOND: Subjects who completed B-LONG or Kids B-LONG were eligible to enroll in the long-term extension study B-YOND; an open-label, non-randomized, global extension study assessing the long-term safety and efficacy of rFIXFc in previously treated subjects with hemophilia B (endogenous FIX activity ≤2% [≤2 IU/dL])

- A total of 120 subjects from B-LONG (n = 93) and Kids B-LONG (n = 27) enrolled in B-YOND
- Subjects received one or more of the following 4 treatment regimens:
  - WP: 20-100 IU/kg every 7 days
  - Individualized interval prophylaxis (IP), 100 IU/kg every 8-16 days or twice monthly
  - MP: dosing further personalized to meet the needs of individual subjects
  - ET
- Inclusion criteria: The study enrolled eligible subjects who completed either the B-LONG (adults and adolescents ≥12 years of age with ≥100 prior EDs to FIX) or Kids B-LONG (children <12 years of age with ≥50 prior EDs to FIX) parent study
- Exclusion criteria: Those with confirmed high-titer inhibitors (≥5 BU/mL)

PUPs B-LONG: Open-label, single-arm, multicenter, phase 3 study investigating the safety and efficacy of rFIXFc in pediatric PUPs with hemophilia B

- Inclusion criteria: Male PUPs age <18 years with hemophilia B (≤2 IU/dL [≤2%] of endogenous FIX activity)
  - A PUP was defined as a patient who had no prior exposure to FIX concentrates, except for up to 3 infusions of commercially available rFIXFc before the confirmation of eligibility and <28 days before screening
- Exclusion criteria:
  - Exposure to blood components or infusion with an FIX concentrate (including plasma derived) other than rFIXFc
  - History of positive inhibitor test
  - History of hypersensitivity reactions associated with any rFIXFc administration
  - Other coagulation disorder in addition to hemophilia B
  - Any concurrent clinically significant major disease

Facilitator Notes

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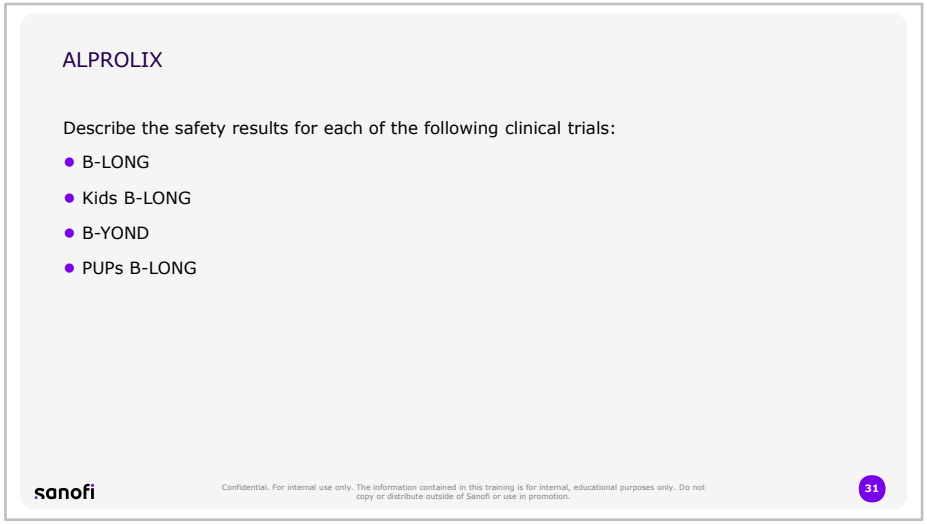
Key Concepts

B-LONG:
- The primary efficacy endpoint was the per-patient ABR
- Additional efficacy endpoints:
  - Pharmacokinetic (PK) measures
  - Weekly dose of rFIXFc (in group 1)
  - Dosing interval (in group 2)
  - Number of injections and dose per injection required to resolve a bleeding episode
  - Rating of hemostasis provided by the site investigator or surgeon during the perioperative period

Kids B-LONG:
- ABR
- Number of infusions and dose per rFIXFc infusion required to resolve bleeding episodes
- Assessments of response to rFIXFc treatment for bleeding episodes

B-YOND:
- ABR
- Total exposure
- Total consumption
- Physician's global assessment of the subject's response to treatment regimen
- Investigator/surgeon assessment of hemostatic response to surgery

PUPs B-LONG:
- ABR
- Number of infusions and rFIXFc dose per infusion required to resolve a bleeding episode
- Total annualized rFIXFc consumption
- Assessment of response to treatment for bleeding episodes by investigator and caregiver
- Physician's global assessment of response to the assigned rFIXFc regimen



Facilitator Notes

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Key Concepts

B-LONG:

- Inhibitors were not detected in any participants with test results that could be evaluated, including 55 participants with 50 or more EDs, for whom the inhibitor incidence was 0% (95% confidence interval [CI], 0-6.5); the inhibitor incidence overall was also 0% (95% CI, 0-3.0)
- Among the 119 participants in groups 1, 2, and 3, a total of 88 (73.9%) had at least one AE during the rFIXFc treatment period (excluding AEs that occurred during the perioperative period); most common AEs (with an incidence ≥5% in a pooled analysis of groups 1, 2, and 3) were: nasopharyngitis, influenza, arthralgia, upper respiratory tract infection, headache, and hypertension

Kids B-LONG:

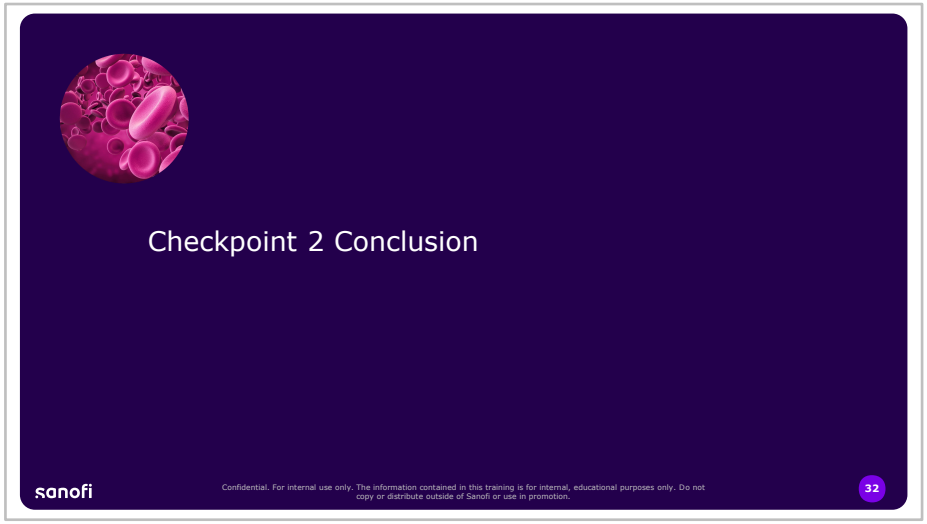
- No patients developed an inhibitor (neutralizing antibody) to rFIXFc
- The reported AEs were typical of the pediatric hemophilia B population; the most common AEs (occurring in ≥20% of the total population) were nasopharyngitis and fall

B-YOND:

- Primary endpoint was occurrence of inhibitor development, with a positive inhibitor defined as a neutralizing antibody value ≥0.6 BU/mL (assessed by Nijmegen-modified Bethesda assay at a central laboratory and confirmed on 2 separate samples within 2-4 weeks)
- AEs

PUPs B-LONG:

- Primary endpoint was the occurrence of inhibitor development, with a positive inhibitor defined as an inhibitor test result of ≥0.60 BU/mL that was confirmed by a second test result of ≥0.60 BU/mL from a separate sample drawn 2-4 weeks after the original sample
- AEs



Key Concepts

- **Address** outstanding questions/concerns.
- **Thank** participants for attending Checkpoint 2.
- **Conclude** the session.

Facilitator Notes