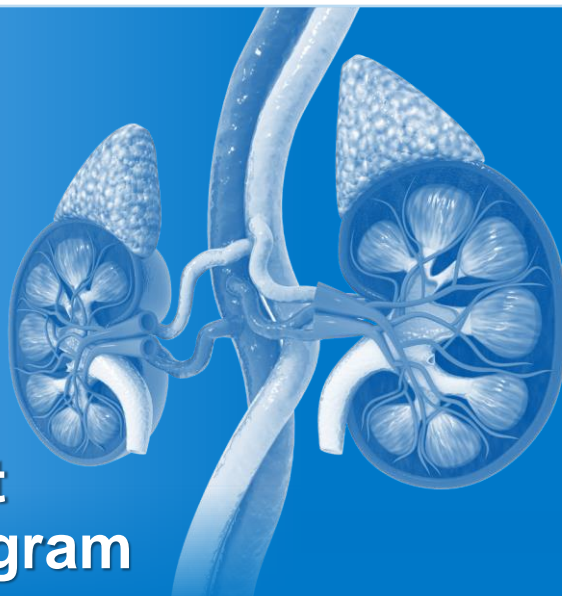




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# Daprodustat Clinical Program Training




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## Facilitator Notes

- **Display** this slide on-screen as participants arrive.
- **Welcome** participants to the Daprodustat Clinical Training.



Daprodustat Clinical Program Training 

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## Disclaimer

This training is intended to help you with your background understanding of the Daprodustat Clinical Program and not to provide selling messages. Information in this training is not appropriate for use in promotion or selling. Only headquarters (HQ)-approved messaging and materials should be used in promotion or selling.

**NOTE: This information is for your background knowledge only and is not approved for use in promotion. HQ-approved messages for use with healthcare providers (HCPs) will be provided in your approved promotional materials. As a reminder, GSK policy requires that all communications with customers about our prescription medicines are truthful, accurate, not misleading, and reflect balance between the medicine's risks and benefits.**

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## Facilitator Notes

**Review** the content on-screen.



**Daprodustat Clinical Program Training**

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## Learning Objectives

**Upon completion of this training, you will be able to:**

- ✓ Explain the mechanism of action of daprodustat
- ✓ Provide an overview of the ASCEND program
- ✓ Discuss the study design and outcomes of the ASCEND-ND, ASCEND-D, ASCEND-NHQ, ASCEND-ID, and ASCEND-TD clinical trials

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## Facilitator Notes

### Say:

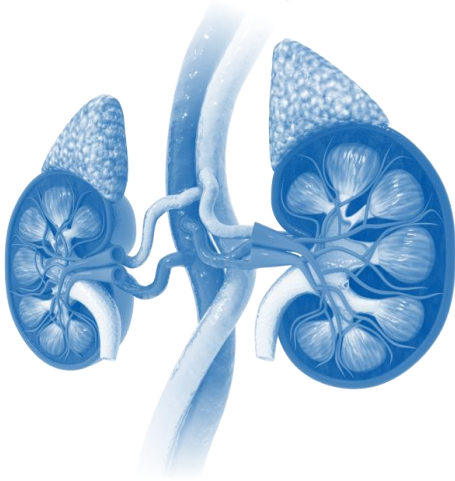
- *Today we will review the daprodustat mechanism of action and the key clinical trials that evaluated the safety and efficacy of daprodustat.*
- *Upon completion of this training, you will be able to:*
  - *Explain the mechanism of action of daprodustat*
  - *Provide an overview of the ASCEND program*
  - *Discuss the study design and outcomes of the ASCEND-ND, ASCEND-D, ASCEND-NHQ, ASCEND-ID, and ASCEND-TD clinical trials*



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## Overview of Daprodustat and the ASCEND Program



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## Facilitator Notes

### Say:

- *Let's begin with an overview of daprodustat and the ASCEND clinical trials.*
- *This section of the review will discuss the mechanism of action of daprodustat and introduce the 5 clinical trials that make up the ASCEND clinical program.*



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### Daprodustat Mechanism of Action

Daprodustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that mimics the body's physiological approach to enhancing endogenous erythropoietin production to raise hemoglobin levels.

Asn, asparagine; HIFα, hypoxia inducible factor-alpha; HIFβ, hypoxia inducible factor-beta; HREs, hypoxia response elements; OH, hydroxyl; p300, transcriptional co-activator p300; PHD, prolyl hydroxylase domain; Pro, proline; VHL, von Hippel-Lindau protein; Ub, ubiquitin.

**The target**

Induces erythropoietin production in the kidney and liver

**HIF pathway in CKD**

Erythropoietin production by the kidney is dysregulated in chronic kidney disease (CKD)

**The agent**

HIF-PHIs stabilize the HIF complex and mimic the physiological response to hypoxia, stimulating erythropoiesis and modulating iron metabolism

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## Facilitator Notes

- Say:**
- *Daprodustat is an oral medication evaluated for the treatment of anemia of chronic kidney disease in adults on dialysis and not on dialysis.*
  - *As you know, anemia of CKD is a consequence of reduced erythropoietin production by damaged kidneys and reduced iron availability required for hemoglobin production. This leads to reduction of erythropoiesis, or red blood cell production, in the bone marrow.*
  - *The HIF pathway plays an important role in orchestrating the physiological response to hypoxia by inducing erythropoietin production in the kidney and liver.*
  - *Recall, HIF proteins are transcription factors activated during hypoxic conditions leading to the expression, or turning on of genes, needed for erythropoiesis, iron metabolism, and iron utilization.*
  - *As CKD progresses, pathophysiologic changes occur that affect the HIF pathway function. This results in the HIF pathway not being adequately activated, with subsequent inadequate stimulation of erythropoietin production and iron modulation.*
  - *Daprodustat addresses an important mechanism of anemia of CKD by activating the HIF pathway.*
  - *Daprodustat belongs to a class of drugs called hypoxia-inducible factor prolyl hydroxylase inhibitors, also known as HIF-PHIs.*
  - *By inhibiting prolyl hydroxylase domain, or PHD, enzymes, daprodustat stabilizes HIF-α molecules and thereby increases the expression of genes involved in erythropoietin production and iron utilization, resulting in increased red blood cell production.*



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### The ASCEND Program

**A**nemia **S**tudies in **C**hronic Kidney Disease: **E**rythropoiesis via a **N**ovel Prolyl Hydroxylase Inhibitor **D**aprodustat (**ASCEND**)

Study	Population	Control	Blinding	N	Duration (Years)
<b>Non-Dialysis</b>					
ASCEND-ND	Non-dialysis, mixed prior ESA use	Darbepoetin alfa	Open-label (Sponsor-blind)	3872	1.86 (P25 1.01, P75 2.69)
ASCEND-NHQ	Non-dialysis, not receiving ESA	Placebo	Double-blind	614	0.5
<b>Dialysis</b>					
ASCEND-D	Dialysis, prior ESA use	ESA	Open-label (Sponsor-blind)	2964	2.48 (P25 2.21, P75 2.89)
ASCEND-ID	Incident dialysis, limited prior ESA use	Darbepoetin alfa	Open-label (Sponsor-blind)	312	1
ASCEND-TD	Hemodialysis, prior ESA use	Epoetin alfa	Double-blind	407	1

- ✓ 5 global phase 3 trials
- ✓ Over 8000 patients with anemia of CKD
- ✓ Dialysis and non-dialysis patients
- ✓ Patients treated and not treated with erythropoiesis-stimulating agents (ESAs)
- ✓ Non-inferiority and cardiovascular outcome trials (CVOTs)

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## Facilitator Notes

### Say:

- *The efficacy and safety of daprodustat for the treatment of anemia of CKD was studied in the Anemia Studies in Chronic Kidney Disease: Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat (ASCEND) program.*
- *The ASCEND program included 5 global phase 3 trials that enrolled over 8000 patients with anemia of CKD.*
- *The trials included patients on and not on dialysis, as well as patients both treated and not treated with erythropoiesis-stimulating agents, or ESAs.*
- *The ASCEND program included non-inferiority and cardiovascular outcomes trials in both dialysis and non-dialysis patients.*
- *Recall that non-inferiority studies are designed to show that a new treatment is not unacceptably less efficacious or less tolerated than an active control standard of care treatment. In other words, they are not designed to show that treatments are equal but rather that they are considered similar to standard of care treatment, in this case, an ESA.*
- *Additionally, participants were required to remain iron replete throughout the trials. This meant having adequate iron stores to meet their functional needs without being iron deficient or in iron overload. Iron replete was defined in the ASCEND-D, ASCEND-ND, ASCEND-ID, and ASCEND-TD trials as a ferritin level >100 ng/mL and a transferrin saturation level >20%, and in the ASCEND-NHQ trial as a ferritin level >50 ng/mL and a transferrin saturation >15%. Patients could receive iron treatment throughout the studies to ensure that they remained iron replete.*



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## Cardiovascular Outcome Trial (CVOT) Study Design

### Disease and Treatment Risks

Anemia of CKD: Higher occurrence of major adverse cardiovascular events (MACE) and cardiovascular mortality

Injectable ESAs: Increased risk of death, MACE, and stroke when administered to target hemoglobin levels >11 g/dL

### CVOTs

ASCEND-ND and ASCEND-D

Adjudicated MACE: Composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke.

Study finish: 664 adjudicated first MACE

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## Facilitator Notes

### Say:

- *Anemia in patients with CKD is associated with higher occurrence of major adverse cardiovascular events (MACE) and cardiovascular mortality. This risk increases with anemia severity.*
- *Injectable ESAs are associated with increased risk of death, MACE, and stroke when administered to target hemoglobin levels greater than 11 g/dL.*
- *The ASCEND program evaluated the effects of daprodustat on MACE in 2 separate cardiovascular outcome trials, ASCEND-ND, which enrolled non-dialysis patients, and ASCEND-D, which enrolled patients undergoing dialysis.*
- *An adjudicated MACE in these trials was defined as the composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke.*
- *Study finish in ASCEND-ND and ASCEND-D was defined as the occurrence of 664 adjudicated first MACE.*



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ASCEND Trials Baseline Characteristics

	DIALYSIS TRIALS						NON-DIALYSIS TRIALS			
	ASCEND-D		ASCEND-ID		ASCEND-TD		ASCEND-ND		ASCEND-NHQ	
	Daprodustat (n=1487)	ESA (n=1477)	Daprodustat (n=157)	Darbepoetin alfa (n=165)	Daprodustat (n=270)	Epoetin alfa (n=137)	Daprodustat (n=1937)	Darbepoetin alfa (n=1935)	Daprodustat (n=307)	Placebo (n=307)
Age, median (yr)	58	59	52	56	60	56	67	67	66	67
Male, n (%)	851 (57)	847 (57)	96 (61)	98 (63)	149 (55)	81 (59)	835 (43)	864 (45)	131 (43)	129 (42)
Race or ethnic group, n (%)										
White	995 (67)	982 (66)	110 (70)	107 (69)	195 (72)	94 (69)	1098 (57)	1055 (54)	197 (64)	195 (64)
Black	228 (15)	233 (16)	16 (10)	13 (8)	49 (18)	32 (23)	183 (9)	185 (10)	44 (14)	47 (15)
Other	264 (18)	262 (18)	31 (20)	35 (22)	20 (7)	9 (7)	656 (34)	695 (36)	66 (22)	65 (21)

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Facilitator Notes

- Say:
- This slide takes an overall look at the demographics of the patient populations in the different ASCEND trials.





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### Dialysis Trials: Patient Characteristics<sup>a</sup>

	ASCEND-D		ASCEND-ID		ASCEND-TD <sup>b</sup>	
	Daprodustat n=1487	ESA n=1477	Daprodustat n=157	Darbepoetin alfa n=155	Daprodustat n=270	Epoetin alfa n=137
Dialysis type at randomization, %						
Hemodialysis	89	89	80	81	100	100
Peritoneal dialysis	11	11	20	19	0	0
Hemoglobin, g/dL	10.3 <sup>c</sup>	10.4 <sup>c</sup>	9.5 <sup>c</sup>	9.5 <sup>c</sup>	10.5 (10.0, 11.0) <sup>d</sup>	10.7 (10.2, 11.3) <sup>d</sup>
Receiving IV iron, %	64	64	67	70	64	73
CV disease history, %	45	45	30	29	41	39

<sup>a</sup>Intent-to-treat population. <sup>b</sup>Based on inclusion criteria, all patients in ASCEND-TD were on HD. <sup>c</sup>Mean value. <sup>d</sup>Median value with interquartile range.

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## Facilitator Notes

### Say:

- *This table reviews the patient characteristics in the ASCEND trials that enrolled patients on dialysis.*
- *Patients in ASCEND-D and ASCEND-ID could be receiving either hemodialysis or peritoneal dialysis. Due to inclusion criteria, all patients enrolled in ASCEND-TD had to be receiving hemodialysis.*
- *Patients in the ASCEND-ID trial tended to have lower hemoglobin levels than patients in ASCEND-D or ASCEND-TD.*



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### Non-Dialysis Trials: Patient Characteristics<sup>a</sup>

	ASCEND-ND		ASCEND-NHQ <sup>b</sup>	
	Daprodustat n=1937	Darbepoetin alfa n=1935	Daprodustat n=307	Placebo n=307
CKD stage, %				
Stage 3	17	19	30	28
Stage 4	45	46	45	45
Stage 5	37	35	24	26
Hemoglobin, g/dL (mean)	9.9	9.8	9.7	9.7
SF-36 Vitality score, mean (SD)	N/A	N/A	50.7 (21.2)	52.2 (21.1)
ESA user at randomization, %	47	47	N/A	N/A
CV disease history, %	37	37	N/A	N/A

<sup>a</sup>Intent-to-treat population. <sup>b</sup>ASCEND-NHQ patients did not have recent ESA use based on inclusion criteria. CV, cardiovascular; SF-36, 36-Item Short Form Health Survey.

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## Facilitator Notes

- Say:**
- *This table reviews the patient characteristics in the ASCEND trials that enrolled non-dialysis patients.*
  - *ASCEND-ND was a cardiovascular outcome trial, which is why cardiovascular disease history is important.*
  - *Patients in the ASCEND-ND trials tended to have higher stage CKD than those in ASCEND-NHQ.*
  - *ASCEND-NHQ evaluated effects on quality of life, measured by the SF-36 Vitality Score.*
  - *Due to inclusion criteria, patients enrolled in ASCEND-NHQ were not receiving an ESA.*



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## ASCEND-ND

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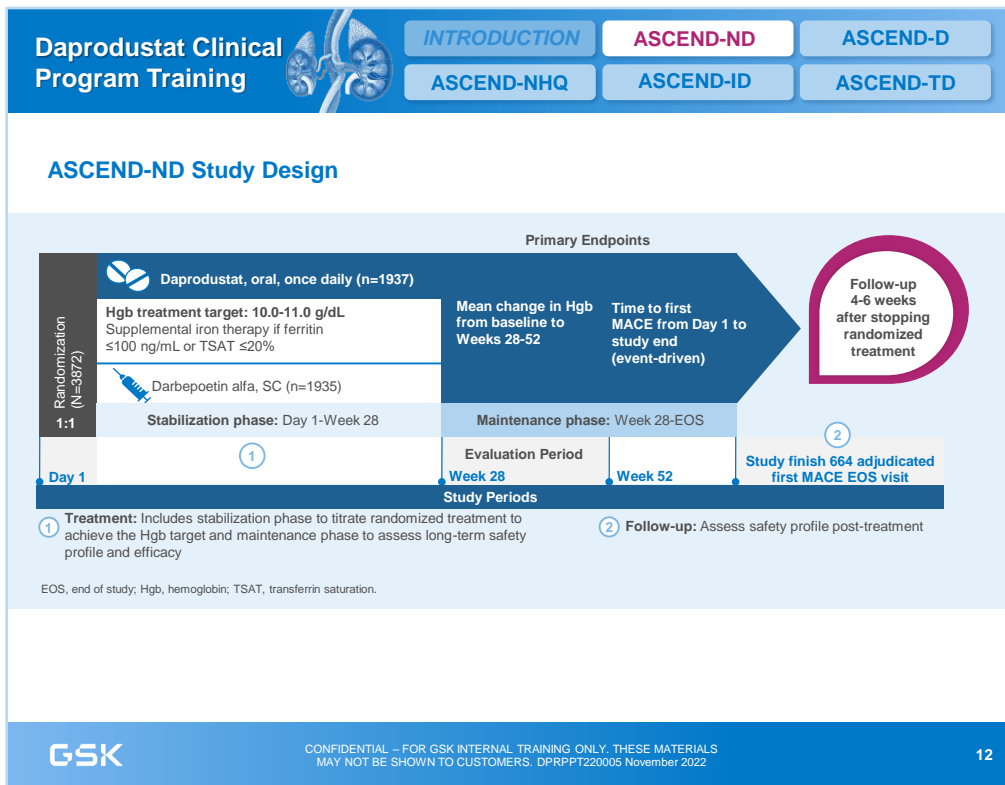
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## Facilitator Notes

### Say:

- *Now that we have reviewed the ASCEND program as a whole, let's take a look at the study design and outcomes of each study individually.*
- *In this section, we will focus on the ASCEND-ND study.*



## Facilitator Notes

### Say:

- ASCEND-ND was a global, randomized, open-label (sponsor blind), active-controlled, event-driven, non-inferiority study.
- The objective was to evaluate the safety and efficacy of daprodustat compared with darbepoetin alfa in patients with anemia of CKD who were not receiving dialysis and were either receiving or not receiving an ESA.
- 3872 patients were randomized 1 to 1 to receive either oral daprodustat once daily or subcutaneous darbepoetin alfa.
- The starting dose of daprodustat was 4 to 12 mg based on the patient's prior ESA dose, with dose adjustments made to a final dose of 1 to 24 mg.
- The starting dose of darbepoetin alfa was based on the patient's prior ESA dose and hemoglobin level at randomization.
- Recall that patients were required to remain iron replete. Iron therapy was given if ferritin was  $\leq 100$  ng/mL or TSAT was  $\leq 20\%$
- Patients first underwent a stabilization phase between Day 1 and Week 28, during which their randomized treatment was titrated to achieve a hemoglobin target between 10 and 11 g/dL. The stabilization phase was followed by a maintenance phase, during which the patient's randomized treatment dose was maintained and the study endpoints were analyzed.
- Follow-up occurred 4 to 6 weeks after stopping randomized treatment to assess the patient's safety profile.
- The study was considered finished after 664 adjudicated first MACE had occurred.



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## Key Study Endpoints

Objectives	Endpoints
<b>Co-primary (tested for non-inferiority)</b>	
<b>Efficacy</b>	Mean change in Hgb from baseline to the average during the primary evaluation period (weeks 28-52)
<b>Safety</b>	First occurrence of an adjudicated MACE (target 664 events)
<b>Principal secondary (tested for superiority, adjusted for multiplicity)</b>	
<b>Safety</b>	CKD progression (40% decline in eGFR, or dialysis for at least 90 days or dialysis that was indicated but not initiated, or kidney transplant) <b>First occurrence of:</b> <ul style="list-style-type: none"> <li>• MACE</li> <li>• MACE or a thromboembolic event</li> <li>• MACE or hospitalization for heart failure</li> </ul>

eGFR, estimated glomerular filtration rate.

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## Facilitator Notes

### Say:

- *ASCEND-ND evaluated daprodustat versus darbepoetin alfa for co-primary non-inferiority endpoints and principal secondary superiority endpoints.*
- *The co-primary endpoints, tested for non-inferiority, were:*
  - *Mean change in hemoglobin from baseline to the average during the primary evaluation period (weeks 28-52); and*
  - *First occurrence of an adjudicated MACE, with a target of 664 events*
- *The principal secondary endpoints, tested for superiority and adjusted for multiplicity, were:*
  - *CKD progression, defined as:*
    - *A 40% decline in estimated glomerular filtration rate; or*
    - *Dialysis for at least 90 days or dialysis that was indicated but not initiated; or*
    - *Kidney transplant*
  - *And first occurrence of MACE, MACE or a thromboembolic event, or MACE or hospitalization for heart failure*



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### Primary Efficacy Endpoint: Hemoglobin Efficacy

**Daprodustat Was Non-Inferior to Darbepoetin Alfa for Mean Change in Hemoglobin from Baseline to the Evaluation Period**

**Mean change in hemoglobin level, g/dL (standard error [SE]):**

- Daprodustat: 0.74 (0.02)
- Darbepoetin alfa: 0.66 (0.02)

**Adjusted mean treatment difference, g/dL (95% CI):**  
0.08 (0.03, 0.13);  $P < 0.001$

**Prespecified non-inferiority margin:**  
-0.75 g/dL

Treatment group	No. of Patients														
Daprodustat	1932	1866	1705	1511	1364	1254	1100	961	832	725	587	453	349	243	
Darbepoetin alfa	1933	1867	1697	1506	1398	1243	1100	952	835	727	602	482	378	272	

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## Facilitator Notes

**Say:**

- In ASCEND-ND, daprodustat met the primary efficacy endpoint, showing non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28 to 52.
- In this graph, the hemoglobin target range for dose changes was 10.0 to 11.0 g/dL. The horizontal lines represent the hemoglobin analysis range (10.0 to 11.5 g/dL), which is an extension of the target range to allow for variability. The bars around each data point indicate 95% confidence intervals.
- Recall, the 95% confidence interval means if the study is completed 100 times, the mean treatment difference would be found within the 95% confidence interval 95 times.
- The mean change in hemoglobin level was 0.74 g/dL for the daprodustat group and 0.66 g/dL for the darbepoetin alfa group.
- The adjusted mean treatment difference during the evaluation period was 0.08 g/dL, which was statistically significant with a P-value <0.001.
- Non-inferiority was achieved because the lower limit of the 95% confidence interval for treatment difference was greater than the prespecified non-inferiority margin of -0.75 g/dL.
- The non-inferiority margin is a prespecified statistical margin by which a new treatment could be worse than a currently accepted treatment but still considered similar. In other words, -0.75 g/dL was the mean hemoglobin difference between daprodustat and ESA treatment considered clinically irrelevant.



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### Primary Safety Endpoint: Cardiovascular Safety

**Daprodustat Was Non-Inferior to Darbeoetin Alfa for Risk of Adjudicated MACE**

Kaplan-Meier Plot of Time to First Adjudicated MACE in ASCEND-ND Study

	Daprodustat (n=1937)	Darbeoetin alfa (n=1935)
First occurrence of adjudicated MACE, n (%)	378 (19.5)	371 (19.2)
Death from any cause	252 (13.0)	259 (13.4)
Non-fatal myocardial infarction	96 (5.0)	91 (4.7)
Non-fatal stroke	30 (1.5)	21 (1.1)

**First adjudicated MACE:**

- Daprodustat: 378 of 1937 (19.5%) patients
- Darbeoetin alfa: 371 of 1935 (19.2%) patients

HR=1.03 (95% CI, 0.89-1.19)

Prespecified non-inferiority margin: HR=1.25

No. at risk											
Daprodustat	1937	1834	1601	1414	1207	1024	840	647	468	288	
Darbeoetin alfa	1935	1825	1582	1412	1221	1038	843	660	474	291	

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## Facilitator Notes

**Say:**

- Daprodustat also met the primary safety endpoint, showing non-inferiority to darbepoetin alfa for risk of adjudicated MACE.
- A first adjudicated MACE occurred in 19.5% of patients in the daprodustat group and 19.2% of patients in the darbepoetin alfa group.
- The hazard ratio for this difference was 1.03.
- Recall a hazard ratio of 1 means there is no difference between the groups. A hazard ratio greater than 1 or less than 1 means that an event happened more in 1 of the groups.
- Non-inferiority was achieved since the upper limit of the 95% confidence interval for the treatment difference was lower than the prespecified non-inferiority margin of 1.25 g/dL.



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### Principal Secondary Endpoints

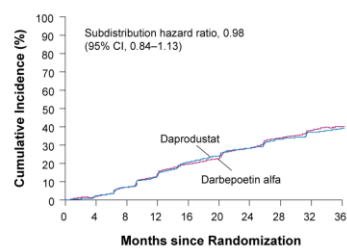
**Cardiovascular Safety**

**Daprodustat Was Not Superior to Darbeoetin Alfa for First Occurrence of MACE, the First Occurrence of MACE or a Thromboembolic Event, and the First Occurrence of MACE or Hospitalization for Heart Failure**

Principal Secondary Endpoints (ITT Population)	HR (95% CI)
MACE	1.03 (0.89-1.19)
MACE or thromboembolic event	1.06 (0.93-1.22)
MACE or hospitalization for heart failure	1.09 (0.95-1.24)

**Progression of CKD**

**Daprodustat Was Not Superior to Darbeoetin Alfa for Progression of CKD**



**Progression of CKD:**

- Daprodustat: 28.1% of patients
- Darbeoetin alfa: 28.4% of patients

Subdistribution HR=0.98 g/dL (95% CI, 0.84-1.13)

No. at Risk										
Daprodustat	1220	1148	966	804	642	535	427	313	211	136
Darbeoetin alfa	1265	1188	994	828	684	570	434	316	224	128

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## Facilitator Notes

**Say:**

- *For the principal secondary endpoints, daprodustat was not superior to darbepoetin alfa for first occurrence of MACE, the first occurrence of MACE or a thromboembolic event, and the first occurrence of MACE or hospitalization for heart failure.*
- *Daprodustat was also not superior to darbepoetin alfa for progression of CKD.*
- *In this study, progression of CKD was defined as:*
  - *A 40% decline in estimated glomerular filtration rate from baseline; or*
  - *End-stage renal disease*
- *Progression of CKD occurred in 28.1% of patients in the daprodustat group and 28.4% of patients in the darbepoetin alfa group.*
- *This study found that daprodustat, as compared with darbepoetin alfa, did not delay progression of CKD.*





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### Safety: Adverse Events

AEs, SAEs, and AEs occurring in  $\geq 10\%$  of patients were **generally similar** between the daprodustat and darbepoetin alfa groups.

AE	Daprodustat n=1937	Darbepoetin alfa n=1933
	No. of patients (%)	No. of patients (%)
Any AE	1545 (79.8)	1487 (76.9)
Any SAE	850 (43.9)	703 (36.4)
<b>AEs occurring in <math>\geq 10\%</math> of patients</b>		
Hypertension	257 (13)	272 (14)
Urinary tract infection	187 (10)	179 (9)
Peripheral edema	199 (10)	166 (9)

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## Facilitator Notes

**Say:**

- *This table reviews the adverse events that were observed in ASCEND-ND.*
- *Adverse events, serious adverse events, and adverse events occurring in greater than or equal to 10% of patients were generally similar between the daprodustat and darbepoetin alfa groups.*
- *79.8% of patients in the daprodustat group and 76.9% of patients in the darbepoetin alfa group experienced any adverse event.*
- *43.9% of patients in the daprodustat group and 36.4% of patients in the darbepoetin alfa group experienced any serious adverse event.*
- *Adverse events that occurred in greater than or equal to 10% of patients included hypertension, urinary tract infection, and peripheral edema.*



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**Safety: Adverse Events of Special Interest**

AESI	Daprodustat n=1937		Darbeoetin alfa n=1933		Relative risk (95% CI)	P value <sup>a</sup>
	No. of patients (%)	No. of events	No. of patients (%)	No. of events		
Thrombosis or tissue ischemia due to excessive erythroipoiesis	5 (0.3)	6	3 (0.2)	3	1.66 (0.40, 6.95)	0.48
Cardiomyopathy	6 (0.3)	6	7 (0.4)	7	0.86 (0.29, 2.54)	0.78
Pulmonary-artery hypertension	15 (0.8)	16	9 (0.5)	11	1.66 (0.73, 3.79)	0.22
Cancer-related death or tumor progression or recurrence	72 (3.7)	82	49 (2.5)	67	1.47 (1.03, 2.10)	0.04
Esophageal or gastric erosions	70 (3.6)	86	41 (2.1)	45	1.70 (1.16, 2.49)	0.005
Proliferative retinopathy, macular edema, or choroidal neovascularization	54 (2.8)	70	44 (2.3)	55	1.22 (0.83, 1.81)	0.31
Exacerbation of rheumatoid arthritis	2 (0.1)	2	4 (0.2)	4	0.50 (0.09, 2.72)	0.41
Worsening of hypertension	344 (17.8)	489	363 (18.8)	519	0.95 (0.83, 1.08)	0.41

<sup>a</sup>The listed unadjusted P values are 2-sided and were calculated with the use of the Cochran-Mantel-Haenszel chi-square test. A P value <0.05 is considered to indicate statistical significance.

In a post hoc analysis using an alternative definition of treatment-emergent adverse events (TEAEs) that took into account the different dosing frequencies of the study treatments, cancer-related mortality and tumor regression and recurrence was 3.7% in the daprodustat group and 3.5% in the darbeoetin group (relative risk [RR]=1.06 [95% CI, 0.76-1.46]); esophageal and gastric erosions was 3.6% in the daprodustat group and 2.5% in the darbeoetin group (RR=1.46 [95% CI, 1.01-2.09]).



**Facilitator Notes**

**Say:**


- *Prespecified adverse events of special interest were generally consistent across the daprodustat and darbeoetin alfa treatment arms, except for cancer-related mortality or tumor progression or recurrence and esophageal or gastric erosions, which were significantly higher for daprodustat.*
- *In a post hoc analysis using an alternative definition of treatment-emergent adverse events that took into account the different dosing frequencies of the study treatments, cancer-related mortality and tumor regression and recurrence was 3.7% in the daprodustat group and 3.5% in the darbeoetin group, which was a relative risk of 1.06 and a 95% confidence interval of 0.76 to 1.46.*
- *Esophageal and gastric erosions was 3.6% in the daprodustat group and 2.5% in the darbeoetin group.*



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## Study Summary



ASCEND-ND


ASCEND-ND was a global, randomized, open-label (sponsor-blind), **active-controlled, event driven, non-inferiority** study.

This study included **3872** patients randomized 1:1 to receive oral **daprodustat** once daily or **injectable darbepoetin alfa**.




Objective

The objective was to evaluate the safety and efficacy of **daprodustat compared with darbepoetin alfa** in patients with anemia of CKD who were **not receiving dialysis** and were either **receiving or not receiving an ESA**.



Results

- Daprodustat met both primary endpoints, demonstrating non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28-52 and first occurrence of adjudicated MACE (target 664 events).
- Daprodustat was not shown to be superior to darbepoetin alfa for principal secondary cardiovascular endpoints or progression of CKD.
- Adverse events were generally similar between the oral daprodustat and injectable darbepoetin alfa groups.



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## Facilitator Notes

### Say:

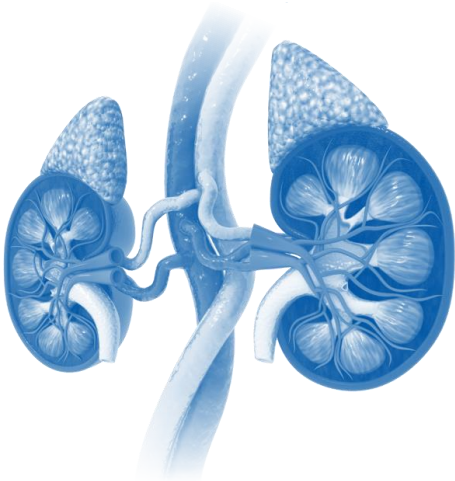
- ASCEND-ND was a global, randomized, open-label (sponsor-blind), active-controlled, event-driven, non-inferiority study.*
- This study included 3872 patients randomized 1:1 to receive oral daprodustat once daily or injectable darbepoetin alfa.*
- The objective was to evaluate the safety and efficacy of daprodustat compared with darbepoetin alfa in patients with anemia of CKD who were not receiving dialysis and were either receiving or not receiving an ESA.*
- Daprodustat met both primary endpoints, demonstrating non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28-52 and first occurrence of adjudicated MACE (target 664 events).*
- Daprodustat was not shown to be superior to darbepoetin alfa for principal secondary cardiovascular endpoints or progression of CKD.*
- Adverse events were generally similar between the oral daprodustat and injectable darbepoetin alfa groups.*



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## ASCEND-D



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## Facilitator Notes

**Say:**

- *Now let's discuss the ASCEND-D study.*



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### ASCEND-D Study Design

**Primary Endpoints**

Randomization (N=2964) 1:1

**Daprodustat, oral, once daily (n=1487)**

Hgb treatment target: 10.0-11.0 g/dL  
Supplemental iron therapy if ferritin ≤100 ng/mL or TSAT ≤20%

**HD: epoetin alfa, IV (n=1477)**  
**PD: darbepoetin alfa, SC**

**Stabilization phase: Day 1-Week 28** | **Maintenance phase: Week 28-EOS**

**Mean change in Hgb from Baseline to Weeks 28-52** | **Time to first MACE from Day 1 to study end (event-driven)**

**Follow-up 4-6 weeks after stopping randomized treatment**

**Day 1** | **Week 28** | **Week 52** | **Study finish 664 adjudicated first MACE EOS visit**

**Study Periods**

① **Treatment:** Includes stabilization phase to titrate randomized treatment to achieve the Hgb target and maintenance phase to assess long-term safety profile and efficacy

② **Follow-up:** Assess safety profile post-treatment

HD, hemodialysis; PD, peritoneal dialysis.

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## Facilitator Notes

- Say:**
- ASCEND-D was a global, randomized, open-label (sponsor blind), active-controlled, event-driven, non-inferiority study.
  - The objective was to evaluate the safety and efficacy of daprodustat compared with an injectable ESA in patients with anemia of CKD on dialysis and being treated with an ESA.
  - In ASCEND-D, 2964 patients were randomized 1 to 1 to receive either oral daprodustat once daily or an ESA.
  - The starting dose of daprodustat was 4 to 12 mg based on the patient's prior ESA dose, with dose adjustments made to a final dose of 1 to 24 mg.
  - Patients in the ESA group received intravenous epoetin alfa if they were receiving hemodialysis and subcutaneous darbepoetin alfa if they were receiving peritoneal dialysis.
  - The ESA dose was based on the patient's prior ESA dose, hemoglobin level at randomization, and type of dialysis being received.
  - Similar to ASCEND-ND, patients were required to remain iron replete throughout the study. They underwent a stabilization phase between Day 1 and Week 28, during which their randomized treatment was titrated to achieve a hemoglobin target between 10 and 11 g/dL. The stabilization phase was followed by a maintenance phase, during which the patient's randomized treatment dose was maintained and the study endpoints were analyzed.
  - Follow-up occurred 4 to 6 weeks after stopping randomized treatment to assess the patient's safety profile.
  - The study was considered finished after 664 adjudicated first MACE had occurred.



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### Key Study Endpoints

Objectives	Endpoints
<b>Co-primary (tested for non-inferiority)</b>	
	<b>Efficacy</b> Mean change in Hgb from baseline to the average during the primary evaluation period (weeks 28-52)
	<b>Safety</b> First occurrence of an adjudicated MACE (target 664 events)
<b>Principal secondary (tested for superiority, adjusted for multiplicity)</b>	
	<b>Efficacy</b> Average monthly IV iron dose up to week 52
	<b>Safety</b> First occurrence of: <ul style="list-style-type: none"> <li>• MACE</li> <li>• MACE or a thromboembolic event</li> <li>• MACE or hospitalization for heart failure</li> </ul>

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## Facilitator Notes

### Say:

- *ASCEND-D evaluated daprodustat versus epoetin alfa or darbepoetin alfa for co-primary non-inferiority endpoints and principal secondary superiority endpoints.*
- *The co-primary endpoints, tested for non-inferiority, were:*
  - *Mean change in hemoglobin from baseline to the average during the primary evaluation period (weeks 28-52); and*
  - *First occurrence of an adjudicated MACE, with a target of 664 events*
- *The principal secondary endpoints, tested for superiority and adjusted for multiplicity, were:*
  - *Average monthly IV iron dose up to week 52; and*
  - *First occurrence of MACE, MACE or a thromboembolic event, or MACE or hospitalization for heart failure*



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### Primary Efficacy Endpoint: Hemoglobin Efficacy

**Daprodustat Was Non-Inferior to an ESA for Change in Hemoglobin from Baseline to the Evaluation Period**

**Mean Hemoglobin Over Time in ASCEND-D Study**

Mean change in hemoglobin level, g/dL (SE):

- Daprodustat: 0.28 (0.02)
- ESA: 0.10 (0.02)

Adjusted mean treatment difference, g/dL (95% CI): 0.18 (0.12, 0.24)

Prespecified non-inferiority margin: -0.75 g/dL

Treatment group	Day 1	Wk 4	Wk 16	Wk 28	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 100	Wk 112	Wk 124	Wk 136	Wk 148
Daprodustat	10.3	10.5	10.6	10.6	10.6	10.6	10.6	10.6	10.6	10.6	10.6	10.6	10.6	10.6
ESA	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3



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## Facilitator Notes

### Say:

- In ASCEND-D, daprodustat met the primary efficacy endpoint, showing non-inferiority to an ESA in mean change in hemoglobin from baseline to weeks 28 to 52.
- In this graph, the hemoglobin target range for dose changes was 10.0 to 11.0 g/dL. The horizontal lines represent the hemoglobin analysis range (10.0 to 11.5 g/dL), which is an extension of the target range to allow for variability. The bars around each data point indicate 95% confidence intervals.
- The mean change in hemoglobin level was 0.28 g/dL for the daprodustat group and 0.10 g/dL for the active comparator ESA groups.
- The adjusted mean treatment difference during the evaluation period was 0.18 g/dL.
- Non-inferiority was achieved because the lower limit of the 95% confidence interval for treatment difference was greater than the prespecified non-inferiority margin of -0.75 g/dL.



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### Primary Safety Endpoint: Cardiovascular Safety

**Daprodustat Was Non-Inferior to an ESA for Adjudicated MACE**

**Kaplan-Meier Plot of Time to First Adjudicated MACE in ASCEND-D (ITT Population)**

	Daprodustat (n=1487)	ESA (n=1477)
First occurrence of adjudicated MACE, n (%)	374 (25.2)	394 (26.7)
Death from any cause	244 (16.4)	233 (15.8)
Non-fatal myocardial infarction	101 (6.8)	126 (8.5)
Non-fatal stroke	29 (2.0)	35 (2.4)

**First adjudicated MACE:**

- Daprodustat: 374 of 1487 (25.2%) patients
- ESA: 394 of 1477 (26.7%) patients

**Hazard ratio (HR)=0.93 (95% CI, 0.81-1.07)**

**Prespecified non-inferiority margin: HR=1.25**

No. at risk										
Daprodustat	1487	1425	1352	1297	1240	1181	1129	861	559	250
ESA	1477	1427	1348	1271	1217	1170	1108	836	525	245

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## Facilitator Notes

- Say:**
- Daprodustat also met the primary safety endpoint, showing non-inferiority to an ESA for risk of adjudicated MACE.*
  - A first adjudicated MACE occurred in 25.2% of patients in the daprodustat group and 26.7% of patients in the ESA group.*
  - The hazard ratio for this difference was 0.93.*
  - Non-inferiority was achieved since the upper limit of the 95% confidence interval for the treatment difference was lower than the prespecified non-inferiority margin of 1.25 g/dL.*





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### Principal Secondary Endpoints

**Daprodustat Was Not Superior to an ESA for First Occurrence of MACE, the First Occurrence of MACE or a Thromboembolic Event, and the First Occurrence of MACE or Hospitalization for Heart Failure**

**Daprodustat Did Not Significantly Reduce Mean Monthly Iron Dose**

#### Cardiovascular Safety

Principal Secondary Endpoints (ITT Population)	HR (95% CI)
MACE	0.93 (0.81-1.07)
MACE or thromboembolic event	0.88 (0.78-1.00)
MACE or hospitalization for heart failure	0.97 (0.85-1.11)

#### Monthly Iron Dose

Means±SE Monthly Dose of IV Iron (ITT Population)

	Daprodustat (n=1487)	ESA (n=1477)
Day 1 – mg±SD	139.2±171.1	137.4±174.7
Week 52 – mg±SD	90.8±3.3	99.9±3.3
Mean difference	-9.1 mg (95% CI, -18.4 to 0.2)	

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## Facilitator Notes

- Say:**
- *For the principal secondary endpoints, daprodustat was not superior to an ESA for first occurrence of MACE, the first occurrence of MACE or a thromboembolic event, and the first occurrence of MACE or hospitalization for heart failure.*
  - *Daprodustat was also not superior to an ESA for mean monthly IV iron dose through week 52.*



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## Safety: Adverse Events

Rates of AEs, SAEs, and AEs occurring in  $\geq 10\%$  of patients were **similar between the daprodustat and ESA groups**

AE	Daprodustat n=1482	ESA n=1474
	No. of patients (%)	No. of patients (%)
Any AE	1307 (88.2)	1252 (84.9)
Any SAE	773 (52.2)	748 (50.7)
<b>AEs occurring in <math>\geq 10\%</math> of patients</b>		
Hypertension	243 (16)	241 (16)
Diarrhea	167 (11)	182 (12)
Dialysis hypotension	141 (10)	110 (7)

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## Facilitator Notes

### Say:

- *This table reviews the adverse events that were observed in ASCEND-D.*
- *Rates of adverse events, serious adverse events, and adverse events occurring in greater than or equal to 10% of patients were similar between the daprodustat and ESA groups.*
- *88.2% of patients in the daprodustat group and 84.9% of patients in the ESA group experienced any adverse event.*
- *52.2% of patients in the daprodustat group and 50.7% of patients in the ESA group experienced a serious adverse event.*
- *Adverse events that occurred in greater than or equal to 10% of patients in the study included hypertension, diarrhea, and dialysis hypotension.*



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Safety: Adverse Events of Special Interest

AESI	Daprodustat n=1482		ESA n=1474		Relative risk (95% CI)
	No. of patients (%)	No. of events	No. of patients (%)	No. of events	
Thrombosis or tissue ischemia due to excessive erythropoiesis	20 (1.3)	30	11 (0.7)	12	1.81 (0.87-3.76)
Cardiomyopathy	15 (1.0)	16	16 (1.1)	17	0.93 (0.46-1.88)
Pulmonary-artery hypertension	9 (0.6)	9	12 (0.8)	13	0.75 (0.32-1.77)
Cancer-related death or tumor progression or recurrence	47 (3.2)	51	51 (3.5)	58	0.92 (0.62-1.35)
Esophageal or gastric erosions	60 (4.0)	75	81 (5.5)	100	0.74 (0.53-1.02)
Proliferative retinopathy, macular edema, or choroidal neovascularization	38 (2.6)	45	35 (2.4)	44	1.08 (0.69-1.70)
Exacerbation of rheumatoid arthritis	2 (0.1)	2	1 (0.1)	1	1.99 (0.18-21.91)
Worsening of hypertension	293 (19.8)	512	302 (20.5)	524	0.96 (0.84-1.11)



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Facilitator Notes

Say:


- Prespecified adverse events of special interest were found to be similar between the daprodustat and ESA groups.



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## Study Summary




ASCEND-D

ASCEND-D was a global, randomized, open-label (sponsor-blind), **active-controlled, event-driven, non-inferiority** study. This study included **2964** patients randomized 1:1 to receive oral **daprodustat** once daily or an **injectable ESA**.




Objective

The objective was to evaluate the safety and efficacy of **daprodustat compared with an injectable ESA** in patients with anemia of CKD on dialysis and being treated with an ESA.



Results

- Daprodustat met the primary endpoints, demonstrating non-inferiority to an ESA in mean change in hemoglobin from baseline to weeks 28-52 and first occurrence of adjudicated MACE.
- Daprodustat was not shown to be superior to an ESA for mean monthly IV iron dose through week 52 or the principal secondary cardiovascular endpoints.
- Safety profiles were similar between the oral daprodustat and ESA groups.



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## Facilitator Notes

### Say:

- ASCEND-D was a global, randomized, open-label (sponsor-blind), active-controlled, event-driven, non-inferiority study.*
- This study included 2964 patients randomized 1:1 to receive oral daprodustat once daily or an injectable ESA.*
- The objective was to evaluate the safety and efficacy of daprodustat compared with an injectable ESA in patients with anemia of CKD on dialysis and being treated with an ESA.*
- Daprodustat met the primary endpoints, demonstrating non-inferiority to an ESA in mean change in hemoglobin from baseline to weeks 28-52 and first occurrence of adjudicated MACE.*
- Daprodustat was not shown to be superior to an ESA for mean monthly IV iron dose through week 52 or the principal secondary cardiovascular endpoints.*
- Safety profiles were similar between the oral daprodustat and ESA groups.*



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## ASCEND-NHQ

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## Facilitator Notes

**Say:**

- *In this section, we'll review the study design and outcomes of ASCEND-NHQ.*



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## ASCEND-NHQ Study Design

Dose adjustments as per prespecified algorithm to maintain target Hgb 11-12 g/dL

Randomization (N=614)  
1:1

Daprodustat, oral, once daily (n=307) (dose range: 1-16 mg)

Hgb treatment target: 11.0-12.0 g/dL  
Supplemental iron therapy if ferritin <50 ng/mL and/or TSAT <15%

Evaluation period

Day 1

Week 24

Week 28

Treatment period

Follow-up visit 4 weeks after stopping randomized treatment

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## Facilitator Notes

### Say:

- *ASCEND-NHQ was a 28-week, randomized, double-blind, placebo-controlled study.*
- *The objective was to evaluate the efficacy, safety, and effects on quality of life of daprodustat compared with placebo in patients with anemia of CKD not receiving dialysis or an ESA.*
- *614 patients were randomized 1 to 1 to receive either oral daprodustat once daily or oral placebo once daily.*
- *The starting dose of daprodustat was 2 to 4 mg based on hemoglobin level, with dose adjustments to a final dose of 1 to 16 mg.*
- *Note that the hemoglobin, ferritin, and TSAT ranges were higher in ASCEND-NHQ compared with other trials within the ASCEND program.*
- *The hemoglobin range in ASCEND-NHQ was 11 to 12 g/dL. This was in alignment with KDIGO guidelines, which state that individualization of therapy is reasonable, as some patients may have improvements in quality of life at a higher hemoglobin concentration.*
- *Recall that the hemoglobin range for all other ASCEND trials was 10 to 11 g/dL.*



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## Key Study Endpoints

Objectives	Endpoints
<b>Primary (tested for superiority)</b>	
<span style="font-weight: bold; font-size: 0.8em;">Efficacy</span>	Mean change in Hgb from baseline to the average during the primary evaluation period (weeks 24-28)
<b>Principal secondary (tested for superiority)</b>	
<span style="font-weight: bold; font-size: 0.8em;">Efficacy</span>	Percent participants having a hemoglobin increase of $\geq 1$ g/dL from baseline to the evaluation period
<span style="font-weight: bold; font-size: 0.8em;">QoL</span>	Mean change in SF-36 vitality domain from baseline to week 28

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## Facilitator Notes

### Say:

- *ASCEND-NHQ evaluated daprodustat versus placebo for superiority in a primary endpoint and principal secondary endpoints.*
- *The primary endpoint, tested for superiority, was mean change in hemoglobin from baseline to the average during the primary evaluation period, weeks 24 to 28.*
- *The principal secondary endpoints, tested for superiority, were:*
  - *Percent of participants having a hemoglobin increase of greater than or equal to 1 g/dL from baseline to the evaluation period; and*
  - *Mean change in the 36-item short form health survey, or SF-36, vitality domain from baseline to week 28*



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### Primary Efficacy Endpoint: Hemoglobin Efficacy

Daprodustat Was Superior to Placebo for Change in Hemoglobin from Baseline to Evaluation Period

**Mean Change in Hemoglobin Level From Baseline to Evaluation Period (Weeks 24-28)**

Daprodustat (n=307)

Placebo (n=307)

Mean change from baseline, g/dL		1.58	0.19
Adjusted mean treatment difference, g/dL (95% CI)		1.40 (1.23, 1.56); P<0.0001	

No. of patients	Baseline	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28
Daprodustat	307	307	307	307	307	307	307	307	307
Placebo	307	307	307	307	307	307	307	307	307

**Legend:**

- ▲ Daprodustat
- Placebo

**Evaluation Period:** Weeks 24-28

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## Facilitator Notes

**Say:**

- In ASCEND-NHQ, daprodustat met the primary endpoint, showing superiority to placebo for mean change in hemoglobin level at weeks 24 to 28.
- The mean change in hemoglobin from baseline to the evaluation period was 1.58 g/dL in the daprodustat group and 0.19 g/dL in the placebo group.
- This was an adjusted mean treatment difference of 1.40 g/dL, which was statistically significant with a P-value less than 0.0001.





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### Principal Secondary Endpoints

#### Hemoglobin Efficacy

Greater Number of Patients Achieved  $\geq 1$  g/dL Increase in Hemoglobin With Daprodustat Than Placebo

Percentage of Participants Having a Hemoglobin Increase of  $\geq 1$  g/dL From Baseline in the Evaluation Period

	Daprodustat (n=307)	Placebo (n=307)
Proportion achieving $\geq 1$ g/dL increase	77%	18%
Adjusted mean treatment difference, % (95% CI)	56% (49%, 63%); $P < 0.0001$	

---

#### Quality of Life

Daprodustat Was Superior to Placebo for Change in SF-36 Vitality Domain Score

- Change in vitality domain scores, mean (SE)
  - Daprodustat: 7.29 (1.12)
  - Placebo: 1.93 (1.16)
- Difference in vitality domain score, mean (95% CI): 5.36 (2.17, 8.56);  $P = 0.0005$

SF-36 Vitality Domain Score Change from Baseline

No. of patients	Wk 8	Wk 12	Wk 28
Daprodustat	307	307	307
Placebo	307	307	307

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## Facilitator Notes

- Say:**
- Daprodustat also met the principal secondary endpoints, showing superiority to placebo.
  - A greater number of patients achieved a greater than or equal to 1 g/dL increase in hemoglobin with daprodustat than placebo.
  - 77% of patients in the daprodustat group achieved a greater than or equal to 1 g/dL increase in hemoglobin, compared with 18% of patients in the placebo group.
  - The adjusted mean treatment difference was 56%, which was statistically significant with a P-value less than 0.0001.
  - Daprodustat was also superior to placebo for change in SF-36 vitality domain score from baseline to week 28.
  - Recall that the SF-36 is a patient-reported questionnaire used in clinical trials that allows patients to answer questions about their health status.
  - ASCEND-NHQ used the SF-36 vitality domain score, which measured fatigue, to evaluate quality of life. The vitality domain of the SF-36 has been shown to be the most relevant to patients with anemia of CKD.
  - The change in vitality domain score was 7.29 for the daprodustat group and 1.93 for the placebo group.
  - The mean difference in vitality domain score was 5.36, which was statistically significant with a P-value of 0.0005.



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### Secondary Endpoint: Vitality Responders

A Greater Proportion of Patients on Daprodustat Achieved a Clinically Meaningful ( $\geq 6$ -point) Increase in SF-36 Vitality Score

	Daprodustat (n=307)	Placebo (n=307)
Patients with $\geq 6$ -point increase in SF-36 vitality score <sup>a</sup>	58%	40%
Difference in response rate (daprodustat-placebo)	13%	
Two-sided 95% CI for difference in response rate	4%–22%	
One-sided P value <sup>b</sup>	0.0049	

<sup>a</sup>SF-36 data include imputed values.  
<sup>b</sup>Analysis was prespecified but not multiplicity adjusted. Treatment group comparisons are based on a Cochran-Mantel-Haenszel test adjusted for treatment group and region. One-sided P value is based on test of null hypothesis: (daprodustat–placebo)  $\leq 0$  vs alternative: difference  $> 0$ .

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## Facilitator Notes

### Say:

- *In another secondary endpoint, a greater proportion of patients receiving daprodustat achieved a clinically meaningful improvement in fatigue, measured as greater than or equal to a 6-point increase in SF-36 vitality score compared with placebo.*
- *Recall, the SF-36 Vitality Domain specifically measures patient-reported changes in fatigue and energy levels.*
- *A within-patient difference of 6 points in SF-36 vitality score has been estimated as minimal clinically important difference through literature review.*
- *A threshold of  $\geq 6$  points was selected as a responder criterion in the ASCEND-NHQ study analysis plan.*
- *In this study, 58% of patients in the daprodustat group had a greater than or equal to 6-point increase in SF-36 vitality score, compared with 40% of patients in the placebo group.*
- *This was a 13% difference in response rate between the daprodustat and placebo groups.*



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### Safety: Adverse Events

AEs, SAEs, and AEs occurring in  $\geq 5\%$  of patients were **similar between the daprodustat and placebo groups.**

AE	Daprodustat n=308	Placebo n=306
	No. of patients (%)	No. of patients (%)
Any AE	213 (69)	216 (71)
Any SAE	62 (20)	68 (22)
<b>AEs occurring in <math>\geq 5\%</math> of patients</b>		
Diarrhea	25 (8)	17 (6)
Hypertension	23 (7)	16 (5)
Peripheral edema	12 (4)	21 (7)
Urinary tract infection	13 (4)	15 (5)
Nausea	14 (5)	5 (2)
Fatigue	2 (<1)	15 (5)

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## Facilitator Notes

### Say:

- *This table reviews the adverse events that were observed in ASCEND-NHQ.*
- *Rates of adverse events, serious adverse events, and adverse events occurring in greater than or equal to 5% of patients were similar between the daprodustat and placebo groups.*
- *69% of patients in the daprodustat group and 71% of patients in the placebo group experienced any adverse event.*
- *20% of patients in the daprodustat group and 22% of patients in the placebo group experienced a serious adverse event.*
- *Adverse events that occurred in greater than or equal to 5% of patients in the study included diarrhea, hypertension, peripheral edema, urinary tract infection, nausea, and fatigue.*



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### Safety: Adverse Events of Special Interest

AESI	Daprodustat n=308	Placebo n=306
	No. of patients (%)	No. of patients (%)
Death, myocardial infarction, stroke, heart failure, PE, DVT, thromboembolic events, thrombosis of vascular access	26 (8)	23 (8)
Pulmonary-artery hypertension	3 (<1)	0
Cancer-related death or tumor progression or recurrence	1 (<1)	2 (<1)
Esophageal or gastric erosions	2 (<1)	3 (<1)
Proliferative retinopathy, macular edema, or choroidal neovascularization	3 (<1)	9 (3)
Exacerbation of rheumatoid arthritis	2 (<1)	0
Worsening of hypertension	31 (10)	26 (8)

DVT, deep vein thrombosis; PE, pulmonary embolism.

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## Facilitator Notes

### Say:


- *Prespecified adverse events of special interest were consistent across the daprodustat and placebo treatment arms.*



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## Study Summary



ASCEND-NHQ


ASCEND-NHQ was a 28-week, randomized, double-blind, placebo-controlled study.

This study included 614 patients randomized 1:1 to receive oral daprodustat once daily or oral placebo.




Objective

The objective was to evaluate the efficacy, safety, and effects on QoL of **daprodustat compared with placebo** in patients with anemia of CKD **not receiving dialysis or ESAs**.



Results

- Daprodustat met the primary endpoint and was superior to placebo for mean change in hemoglobin level at weeks 24-28.
- A greater proportion of patients treated with daprodustat had a  $\geq 1$  g/dL increase in hemoglobin from baseline compared with placebo at weeks 24-28.
- Daprodustat was shown to be superior to placebo for change in SF-36 vitality domain score from baseline to week 28
- Safety profiles were similar between the oral daprodustat and placebo groups.



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## Facilitator Notes

### Say:

- ASCEND-NHQ was a 28-week, randomized, double-blind, placebo-controlled study.*
- This study included 614 patients randomized 1:1 to receive oral daprodustat once daily or oral placebo.*
- The objective was to evaluate the efficacy, safety, and effects on quality of life of daprodustat compared with placebo in patients with anemia of CKD not receiving dialysis or an ESA.*
- Daprodustat met the primary endpoint and was superior to placebo for mean change in hemoglobin level at weeks 24 to 28.*
- Daprodustat also met principal secondary efficacy and quality of life endpoints.*
- A greater proportion of patients treated with daprodustat had a greater than or equal to 1 g/dL increase in hemoglobin from baseline compared with placebo at weeks 24 to 28.*
- Daprodustat was shown to be superior to placebo for change in SF-36 vitality domain score from baseline to week 28.*
- Additionally, a greater proportion of patients on daprodustat achieved a clinically meaningful improvement in fatigue, measured as a  $\geq 6$ -point increase in SF-36 vitality score compared with placebo.*
- Safety profiles were similar between the oral daprodustat and placebo groups.*



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## ASCEND-ID

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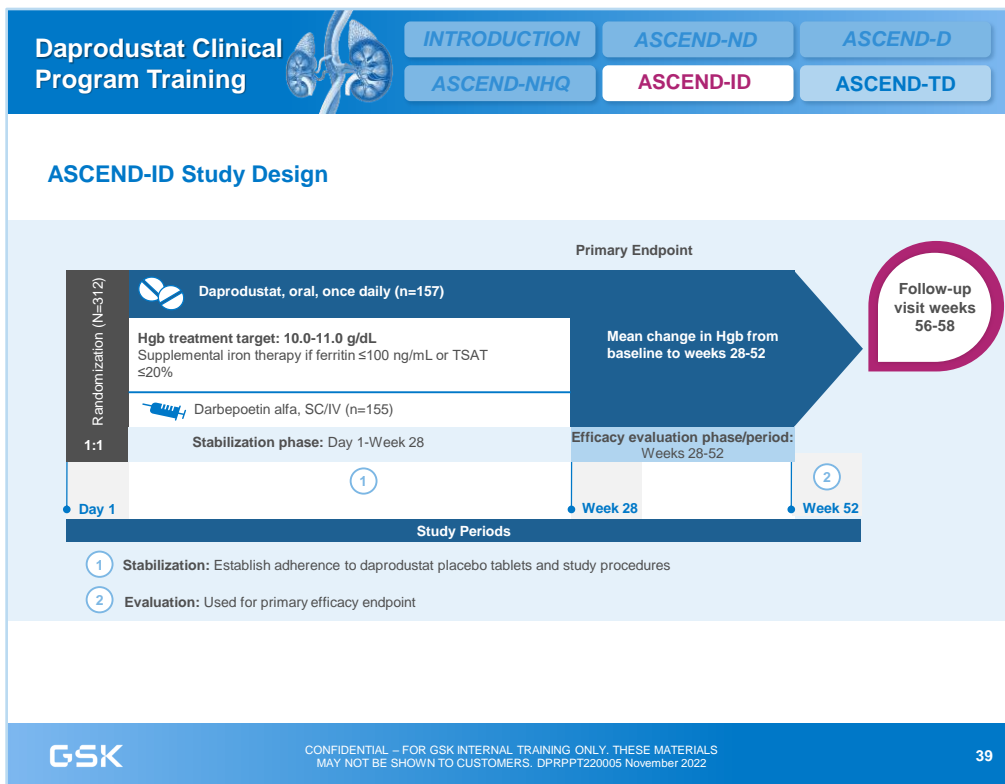
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## Facilitator Notes

### Say:

- *Now we will review the ASCEND-ID study.*
- *ID is short for incident dialysis.*
- *While the ASCEND-D trial enrolled patients on dialysis who were established and physiologically stable, the ASCEND-ID trial enrolled patients receiving incident dialysis, which is typically defined as dialysis initiated within the past 90 to 120 days.*
- *This is important because patients with advanced CKD with an imminent dialysis start or those who have recently initiated hemodialysis or peritoneal dialysis within 90 to 120 days are at very high risk of morbidity and mortality.*



## Facilitator Notes

### Say:

- *ASCEND-ID was a 52-week, global, randomized, open-label (sponsor-blind), active-control group, non-inferiority study.*
- *The objective was to evaluate the safety and efficacy of daprodustat compared with darbepoetin alfa in patients with anemia of CKD who recently initiated hemodialysis or peritoneal dialysis.*
- *312 patients were randomized 1 to 1 to receive either oral daprodustat once daily or intravenous or subcutaneous darbepoetin alfa.*
- *The starting dose of daprodustat was 1 to 4 mg based on hemoglobin level, with dose adjustments made to a final dose of 1 to 24 mg.*
- *Patients in the darbepoetin alfa group received 40 to 60 mg every 2 or 4 weeks intravenously if the patient was receiving hemodialysis and subcutaneously if the patient was receiving peritoneal dialysis.*
- *Patients underwent a stabilization phase between Day 1 and Week 28, during which their randomized treatment was titrated to achieve a hemoglobin target between 10 and 11 g/dL. The stabilization phase was followed by an efficacy evaluation phase from weeks 28 to 52, during which the primary efficacy endpoint was evaluated.*
- *A follow-up visit occurred between weeks 56 to 58.*



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## Key Study Endpoints

Objectives	Endpoints
<b>Primary (tested for non-inferiority)</b>	
<b>Efficacy</b>	Mean change in Hgb from baseline to the average during the primary evaluation period (weeks 28-52)
<b>Principal secondary (tested for superiority)</b>	
<b>Efficacy</b>	Average monthly IV iron dose (mg)/patient from baseline to week 52

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## Facilitator Notes

- Say:**
- *ASCEND-ID evaluated daprodustat versus darbepoetin alfa for 1 primary non-inferiority endpoint and 1 principal secondary superiority endpoint.*
  - *The primary endpoint, tested for non-inferiority, was mean change in hemoglobin from baseline to the average during the primary evaluation period (weeks 28 to 52).*
  - *The principal secondary endpoint, tested for superiority, was the average monthly intravenous iron dose per patient from baseline to week 52.*





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### Primary Efficacy Endpoint: Hemoglobin Efficacy

**Daprodustat Was Non-Inferior to Darbeoetin Alfa for Change in Hemoglobin From Baseline to Weeks 28-52**

#### Mean Hemoglobin Level Over Time

Mean change in hemoglobin level, g/dL (SE):

- Daprodustat: 1.02 (0.09)
- Darbeoetin alfa: 1.12 (0.09)

Mean treatment difference, g/dL (95% CI): -0.10 (-0.34, 0.14)

Prespecified non-inferiority margin: -0.75

Patients, No.	SCR	Day 1	BL	4	8	12	16	20	24	28	32	36	40	44	48	52	FU	
Daprodustat	157	157	157	157	157	157	157	157	157	157	157	157	157	157	157	157	157	117
Darbeoetin alfa	155	155	155	155	155	155	155	155	155	155	155	155	155	155	155	155	155	107

BL, baseline; FU, follow-up; SCR, screening; wk, week.

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## Facilitator Notes

**Say:**

- *In ASCEND-ID, daprodustat met the primary efficacy endpoint, showing non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28 to 52.*
- *The mean change in hemoglobin level was 1.02 g/dL for the daprodustat group and 1.12 g/dL for the darbepoetin alfa group.*
- *The adjusted mean treatment difference during the evaluation period was -0.10 g/dL.*
- *Non-inferiority was achieved because the lower limit of the 95% confidence interval for treatment difference was greater than the prespecified non-inferiority margin of -0.75 g/dL.*



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### Principal Secondary Endpoint: IV Iron Use

Daprodustat Was Not Superior to Darbepoetin Alfa for IV Iron Use from Baseline to Week 52

	Daprodustat (n=157)	Darbepoetin alfa (n=155)
Baseline – mg±SD	159.3±207.1	180.1±209.9
Week 52 – mg±SD	142.0±161.0	128.0±137.0
Mean difference	19.4 mg (95% CI, -11.0 to 49.9)	

No. of patients	157	156	146	133	114
Daprodustat	157	156	146	133	114
Darbepoetin alfa	155	154	143	135	122

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## Facilitator Notes

- Say:**
- *For the principal secondary endpoint, daprodustat was not shown to be superior to darbepoetin alfa for change from baseline in mean monthly IV iron up to week 52.*
  - *The mean difference in average monthly dose of intravenous iron during the evaluation period was 19.4 mg.*



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Safety: Adverse Events

AEs, SAEs, and AEs occurring in ≥5% of patients were **similar between the daprodustat and darbepoetin alfa groups.**

AE	Daprodustat n=157	Darbepoetin alfa n=155
	No. of patients (%)	No. of patients (%)
Any AE	120 (76)	112 (72)
Any SAE	52 (33)	51 (33)
<b>AEs occurring in ≥5% of patients</b>		
Hypertension	29 (18)	25 (16)
Dialysis hypotension	21 (13)	15 (10)
Diarrhea	14 (9)	11 (7)
Fluid overload	14 (9)	9 (6)
Headache	12 (8)	9 (6)
Upper respiratory tract infection	7 (4)	11 (7)
Hypotension	7 (4)	9 (6)
Muscle spasms	7 (4)	9 (6)
Nasopharyngitis	7 (4)	9 (6)

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## Facilitator Notes

**Say:**

- *This table reviews the adverse events that were observed in ASCEND-ID.*
- *Rates of adverse events, serious adverse events, and adverse events occurring in greater than or equal to 5% of patients were similar between the daprodustat and darbepoetin alfa groups.*
- *76% of patients in the daprodustat group and 72% of patients in the darbepoetin alfa group experienced any adverse event.*
- *33% of patients in the daprodustat group and 33% of patients in the darbepoetin alfa group experienced a serious adverse event.*
- *Adverse events that occurred in greater than or equal to 5% of patients in the study included hypertension, dialysis hypotension, diarrhea, fluid overload, headache, upper respiratory tract infection, hypotension, muscle spasms, and nasopharyngitis.*



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### Safety: Adverse Events of Special Interest

AESI	Daprodustat n=157		Darbepoetin alfa n=155	
	No. of patients (%)	Rate per 100 person-years	No. of patients (%)	Rate per 100 person-years
Death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access	27 (17)	24.67	27 (17)	23.67
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	0	0	1 (<1)	0.79
Cardiomyopathy	0	0	2 (1)	1.59
Pulmonary-artery hypertension	1 (<1)	0.85	0	0
Cancer-related death or tumor progression or recurrence	1 (<1)	0.84	3 (2)	2.38
Esophageal or gastric erosions	1 (<1)	0.84	3 (2)	2.39
Proliferative retinopathy, macular edema, or choroidal neovascularization	4 (3)	3.4	1 (<1)	9.79
Exacerbation of rheumatoid arthritis	0	0	0	0
Worsening of hypertension	38 (24)	38.36	29 (19)	26.48

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## Facilitator Notes

### Say:


- *Prespecified adverse events of special interest were consistent across the daprodustat and darbepoetin alfa treatment arms, except for worsening of hypertension, which was higher in the daprodustat arm.*
- *Note that although there was a higher percentage of worsening hypertension in the daprodustat arm, the objective blood pressure values were similar.*



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## Study Summary



ASCEND-ID


ASCEND-ID was a 52-week, global, randomized, **open-label (sponsor-blind), active-controlled, non-inferiority** study.

This study included 312 patients randomized 1:1 to receive oral **daprodustat** once daily or IV/SC **darbepoetin alfa**.




Objective

The objective was to evaluate the safety and efficacy of **daprodustat compared with darbepoetin alfa** in patients with anemia of CKD **who recently initiated hemodialysis or peritoneal dialysis**.



Results

- Daprodustat met the primary endpoint, demonstrating non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28-52.
- Daprodustat was not shown to be superior to darbepoetin alfa for change from baseline in mean monthly IV iron up to week 52.
- Adverse events were generally similar between the oral daprodustat and darbepoetin alfa groups.



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## Facilitator Notes

### Say:

- ASCEND-ID was a 52-week, global, randomized, open-label (sponsor-blind), active-controlled, non-inferiority study.*
- This study included 312 patients randomized 1:1 to receive oral daprodustat once daily or darbepoetin alfa intravenous or subcutaneous based on the type of dialysis the patient was receiving.*
- The objective was to evaluate the safety and efficacy of daprodustat compared with darbepoetin alfa in patients with anemia of CKD who recently initiated hemodialysis or peritoneal dialysis.*
- Daprodustat met the primary endpoint, demonstrating non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28-52.*
- For the principal secondary endpoint, daprodustat was not shown to be superior to darbepoetin alfa for change from baseline in mean monthly intravenous iron up to week 52.*
- Adverse events were generally similar between the oral daprodustat and darbepoetin alfa groups.*



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## ASCEND-TD

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## Facilitator Notes

### Say:

- *Lastly, let's look at the study design and outcomes of ASCEND-TD.*
- *The ASCEND-TD study is the only study in the ASCEND program where daprodustat was given 3 times per week.*
- *Remember that hemodialysis is usually given in a dialysis clinic 3 times per week, with short-acting ESAs, such as epoetin alfa, administered intravenously during a patient's dialysis session.*
- *As part of the double-blind, double-dummy trial design, participants received both oral tablets (daprodustat or placebo) and IV infusion (ESA or placebo) in both treatment groups to correspond with dialysis sessions.*



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## ASCEND-TD Study Design

**ASCEND-TD Study Design**  
Dose adjustments as per prespecified algorithm to maintain target Hgb 10-11 g/dL

The diagram illustrates the study design timeline. It begins with randomization (N=407) at Day 1. The study is divided into two groups: Daprodustat, oral TIW (n=270) with a dose range of 2-48 mg, and Epoetin alfa, IV once weekly/TIW (n=137) with a total weekly dose range of 1500-60,000 units. The timeline is split into a 2:1 ratio. The first 28 weeks are the stabilization period, followed by a 24-week evaluation period from Week 28 to Week 52. A treatment period is indicated to maintain hemoglobin between 10 and 11 g/dL. A callout box indicates a follow-up visit 4 weeks after stopping randomized treatment at Week 52.

TIW, three times per week.  
\*Period during which treatment will be dose-titrated to achieve the hemoglobin target.

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## Facilitator Notes

### Say:

- ASCEND-TD was a 52-week, double-blind, randomized, active-controlled, double-dummy, parallel-group, multicenter, non-inferiority study.
- The objective was to evaluate the safety and efficacy of daprodustat administered 3-times-weekly compared with intravenous epoetin alfa in patients with anemia of CKD receiving hemodialysis.
- 407 patients were randomized 2 to 1 to receive either:
  - Oral daprodustat 3 times weekly with intravenous saline; or
  - Intravenous epoetin alfa once weekly or 3-times-weekly, depending on the dose level, with oral placebo.
- The starting dose of daprodustat was based on the patient's previous ESA dose and was adjusted to a final dose of 2 to 48 mg.
- Patients receiving intravenous epoetin alfa were titrated to a dose range of 1500 to 60,000 units per week.
- Patients enrolled in ASCEND-TD underwent a stabilization phase between Day 1 and week 28, during which their randomized treatment was titrated to achieve a hemoglobin target between 10 and 11 g/dL. The stabilization phase was followed by an evaluation phase from weeks 28 to 52, during which the primary endpoint was analyzed. Patients underwent a follow-up visit 4 weeks after stopping randomized treatment.



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## Key Study Endpoints

				Endpoints
<b>Primary (tested for non-inferiority)</b>				
	<b>Efficacy</b>			Mean change in Hgb from baseline to the average during the primary evaluation period (weeks 28-52)
<b>Principal secondary (tested for superiority)</b>				
	<b>Efficacy</b>			Average monthly IV iron dose (mg)/patient from baseline to week 52

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## Facilitator Notes

### Say:

- *ASCEND-TD evaluated daprodustat versus epoetin alfa for 1 primary non-inferiority endpoint and 1 principal secondary superiority endpoint.*
- *The primary endpoint, tested for non-inferiority, was mean change in hemoglobin from baseline to the average during the primary evaluation period (weeks 28 to 52).*
- *The principal secondary endpoint, tested for superiority, was the average monthly intravenous iron dose from baseline to week 52.*





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### Primary Efficacy Endpoint: Hemoglobin Efficacy

**Daprodustat Three-Times Weekly Was Non-Inferior to Epoetin Alfa for Mean Change in Hemoglobin From Baseline to the Evaluation Period**

**Mean Change in Hemoglobin Level From Baseline to Evaluation Period (Weeks 28-52)**

Visit	Daprodustat (g/dL)	Epoetin alfa (g/dL)
SCR WK-4	10.6	10.4
DAY 1	10.6	10.4
W1	10.6	10.4
W2	10.6	10.4
W4	10.6	10.4
W8	10.6	10.4
W12	10.6	10.4
W16	10.6	10.4
W20	10.6	10.4
W24	10.6	10.4
W28	10.6	10.4
W32	10.6	10.4
W36	10.6	10.4
W40	10.6	10.4
W44	10.6	10.4
W48	10.6	10.4
W52	10.6	10.4
Follow-up	10.6	10.4

**Mean change in hemoglobin level, g/dL (SE):**

- Daprodustat: -0.04 (0.045)
- Epoetin alfa: 0.02 (0.066)

**Mean treatment difference, g/dL (95% CI):** -0.05 (-0.21, 0.10)

**Prespecified non-inferiority margin:** -0.75

No. of patients	270	270	270	270	270	270	270	270	270	270	270	270	270	270	270	166	
Daprodustat	137	137	137	137	137	137	137	137	137	137	137	137	137	137	137	137	79
Epoetin alfa																	

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## Facilitator Notes

- Say:**
- *In ASCEND-TD, daprodustat 3-times-weekly met the primary efficacy endpoint, showing non-inferiority to epoetin alfa in mean change in hemoglobin from baseline to weeks 28 to 52.*
  - *The mean change in hemoglobin level was -0.04 g/dL for the daprodustat 3-times weekly group and 0.02 g/dL for the epoetin alfa group.*
  - *The adjusted mean treatment difference during the evaluation period was -0.05 g/dL.*
  - *Non-inferiority was achieved because the lower limit of the 95% confidence interval for treatment difference was greater than the prespecified non-inferiority margin of -0.75 g/dL.*



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### Principal Secondary Endpoint: IV Iron Dose

**Daprodustat Three-Times Weekly Did Not Significantly Reduce Monthly IV Iron Dose Compared With Epoetin Alfa**

Average monthly dose of IV iron from baseline to week 52

	Daprodustat (n=270)	Epoetin alfa (n=137)
Mean baseline monthly IV iron dose – mg (SD)	185.7 (281.7)	175.4 (177.7)
Adjusted mean average monthly IV iron dose during day 1 to week 52 – mg (SE) <sup>a</sup>	98.1±11.0 mg	106.2±15.6 mg
Adjusted mean treatment difference <sup>a</sup>	-8.1 mg (95% CI, -45.7 to 29.4)	

ANCOVA, analysis of covariance.  
<sup>a</sup>Based on ANCOVA model with terms for treatment, baseline monthly IV iron dose, and region. One-sided p-value based on test of null hypothesis: (daprodustat-epoetin) ≥0 vs alternative: difference <0.

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## Facilitator Notes

**Say:**

- *In the principal secondary endpoint, daprodustat 3-times-weekly did not significantly reduce monthly IV iron dose compared with epoetin alfa.*
- *The adjusted average monthly IV iron dose from baseline to week 52 was 98.1 mg in the daprodustat group and 106.2 mg in the epoetin alfa group.*
- *The adjusted mean treatment difference was -8.1 mg, showing no significant reduction in average monthly IV iron dose with 3-times-weekly administration of daprodustat compared with epoetin alfa.*



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### Safety: Adverse Events

AEs, SAEs, and AEs occurring in  $\geq 10\%$  of patients were **similar between the daprodustat and epoetin alfa groups.**

AE	Daprodustat n=270	Epoetin alfa n=136
	No. of patients (%)	No. of patients (%)
Any AE	203 (75)	107 (79)
Any SAE	80 (30)	47 (35)
<b>AEs occurring in <math>\geq 10\%</math> of patients</b>		
Hypertension	24 (9)	15 (11)
Diarrhea	24 (9)	14 (10)
Vomiting	15 (6)	14 (10)
Headache	12 (4)	13 (10)

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## Facilitator Notes

- Say:**
- *This table reviews the adverse events that were observed in ASCEND-TD.*
  - *Rates of adverse events, serious adverse events, and adverse events occurring in greater than or equal to 10% of patients were similar between the daprodustat and epoetin alfa groups.*
  - *75% of patients in the daprodustat group and 79% of patients in the epoetin alfa group experienced any adverse event.*
  - *30% of patients in the daprodustat group and 35% of patients in the epoetin alfa group experienced a serious adverse event.*
  - *Adverse events that occurred in greater than or equal to 10% of patients in the study included hypertension, diarrhea, vomiting, and headache.*



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### Safety: Adverse Events of Special Interest

AESI	Daprodustat n=270	Epoetin alfa n=136
	No. of patients (%)	No. of patients (%)
Death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access	52 (19)	27 (20)
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	1 (<1)	0
Cardiomyopathy	1 (<1)	1 (<1)
Pulmonary-artery hypertension	1 (<1)	1 (<1)
Cancer-related death or tumor progression or recurrence	3 (1)	2 (1)
Esophageal or gastric erosions	7 (3)	2 (1)
Proliferative retinopathy, macular edema, or choroidal neovascularization	5 (2)	1 (<1)
Exacerbation of rheumatoid arthritis	0	0
Worsening of hypertension	33 (12)	20 (15)

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## Facilitator Notes

**Say:**


- *Prespecified adverse events of special interest were consistent across the daprodustat and epoetin alfa treatment arms.*



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## Study Summary



ASCEND-TD


ASCEND-TD was a 52-week, **double-blind**, randomized, active-controlled, double-dummy, parallel-group, multicenter, non-inferiority study.

This study included **407** patients randomized **2:1** to receive oral **daprodustat 3 times weekly** or **epoetin alfa once weekly** or **3 times weekly**.




Objective

The objective was to evaluate the safety and efficacy of **daprodustat administered 3 times weekly** compared with **IV epoetin alfa** in patients with anemia of CKD **receiving hemodialysis**.



Results

- Daprodustat met the primary endpoint, demonstrating non-inferiority to epoetin alfa for mean change in hemoglobin level from baseline to weeks 28-52.
- Daprodustat did not significantly reduce the average monthly dose of IV iron compared with epoetin alfa.
- Safety profiles were similar between the oral daprodustat and epoetin alfa groups.



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## Facilitator Notes

### Say:

- ASCEND-TD was a 52-week, double-blind, randomized, active-controlled, double-dummy, parallel-group, multicenter, non-inferiority study.*
- This study included 407 patients randomized 2:1 to receive oral daprodustat 3-times-weekly or epoetin alfa once weekly or 3 times weekly.*
- The objective was to evaluate the safety and efficacy of daprodustat administered 3-times-weekly compared with intravenous epoetin alfa in patients with anemia of CKD receiving hemodialysis.*
- Daprodustat met the primary endpoint, demonstrating non-inferiority to epoetin alfa for mean change in hemoglobin level from baseline to weeks 28-52.*
- For the principal secondary endpoint, daprodustat did not significantly reduce the average monthly dose of intravenous iron compared with epoetin alfa.*
- Safety profiles were similar between the oral daprodustat and epoetin alfa groups.*



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## ASCEND Program Summary

	DIALYSIS TRIALS			NON-DIALYSIS TRIALS	
	ASCEND-D	ASCEND-ID	ASCEND-TD	ASCEND-ND	ASCEND-NHQ
<b>Comparator</b>	Daprodustat once daily vs. IV epoetin alfa or SC darbepoetin alfa	Daprodustat once daily vs. darbepoetin alfa (IV/SC)	Daprodustat 3 times weekly with IV saline vs. IV epoetin alfa once weekly or 3 times weekly with oral placebo	Daprodustat once daily vs. darbepoetin alfa (SC)	Daprodustat once daily vs. oral placebo
<b>Outcomes</b>	Daprodustat demonstrated non-inferiority to an ESA in mean change in hemoglobin from baseline to weeks 28-52 and for first occurrence of adjudicated MACE.	Daprodustat demonstrated non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28-52.	Daprodustat demonstrated non-inferiority to epoetin alfa for mean change in hemoglobin level from baseline to weeks 28-52.	Daprodustat demonstrated non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28-52 and for first occurrence of adjudicated MACE.	Daprodustat demonstrated superiority to placebo for mean change in hemoglobin level at weeks 24-26.
<b>Principal Secondary Endpoint(s)</b>	Daprodustat did not show superiority to an ESA for cardiovascular endpoints or mean monthly IV iron dose through week 52.	Daprodustat did not show superiority to darbepoetin alfa for change from baseline in mean monthly IV iron up to week 52.	Daprodustat did not significantly reduce monthly IV iron dose compared with epoetin alfa.	Daprodustat did not show superiority for principal secondary cardiovascular endpoints or progression of CKD.	Daprodustat was superior to placebo for number of patients who achieved a $\geq 1$ g/dL increase in hemoglobin from baseline and change in SF-36 vitality domain score from baseline.
<b>Adverse Events</b>	Similar between oral daprodustat and ESA groups.	Generally similar between oral daprodustat and darbepoetin alfa groups.	Similar between oral daprodustat and epoetin alfa groups.	Generally similar between oral daprodustat and injectable darbepoetin alfa.	Similar between oral daprodustat and placebo groups.

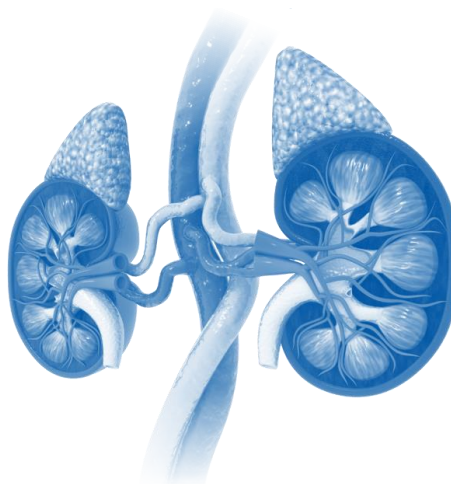
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## Facilitator Notes

- Say:**
- *This slide summarizes the ASCEND program.*
  - *Daprodustat is an oral HIF-PHI evaluated for the treatment of anemia of CKD in adults.*
  - *The ASCEND program includes 5 global phase 3 trials that included over 8,000 patients with anemia of CKD. The trials included patients on and not on dialysis, as well as patients both treated and not treated with current standard of care therapy, ESAs.*
  - *As we know, anemia of CKD is associated with a high occurrence of major cardiovascular events, or MACE, and cardiovascular mortality, and this risk increases with anemia severity.*
  - *The ASCEND program compared the efficacy and safety of daprodustat to an ESA in 2 non-inferiority, cardiovascular outcome trials. ASCEND-ND enrolled patients not on dialysis and ASCEND-D enrolled patients on dialysis.*
  - *Daprodustat met all primary endpoints across each of the 5 trials.*
  - *Specifically, in ASCEND-ND and ASCEND-D, daprodustat met the co-primary endpoints demonstrating non-inferiority to the active comparator ESAs in mean hemoglobin change from baseline and in first occurrence of adjudicated MACE.*
  - *Safety profiles were generally similar between treatment arms across all 5 trials.*



## Thank You!



## Facilitator Notes

- **Address** outstanding questions/concerns.
- **Thank** participants for attending the review presentation.
- **Conclude** the session.