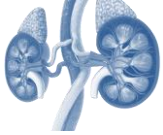
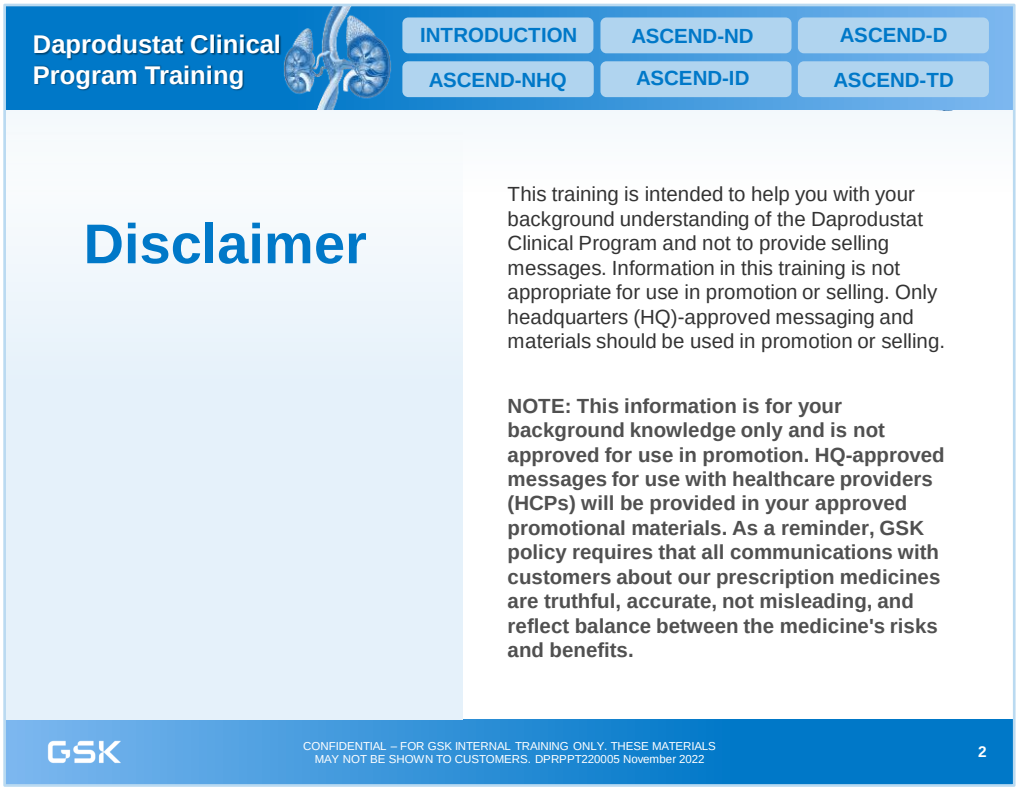
Facilitator Notes

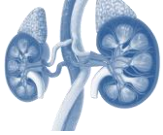
- **Display** this slide on-screen as participants arrive.
- **Welcome** participants to the Daprodustat Clinical Training.

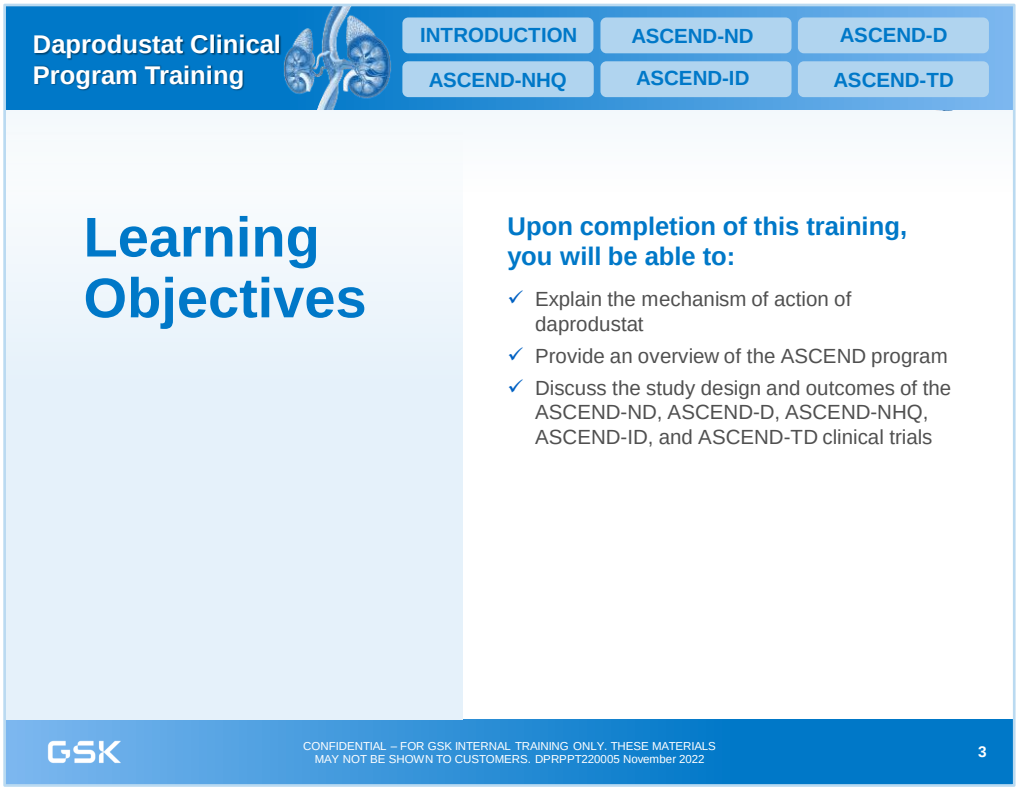




Facilitator Notes

Review the content on-screen.

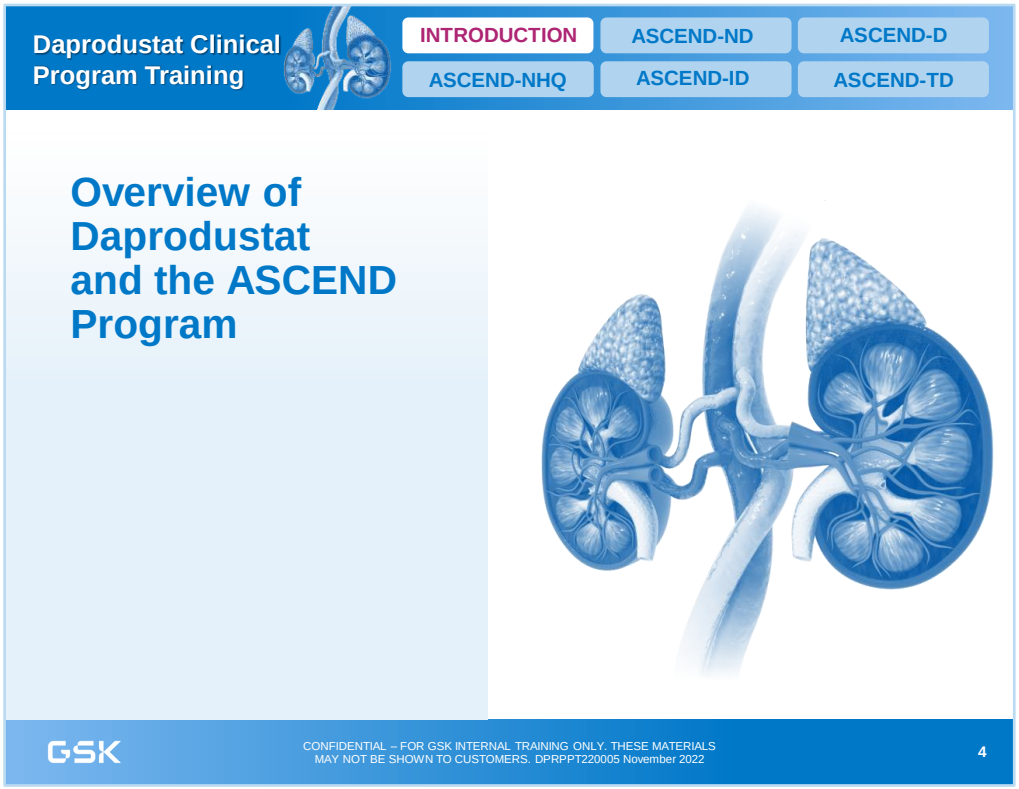




Facilitator Notes

Say:

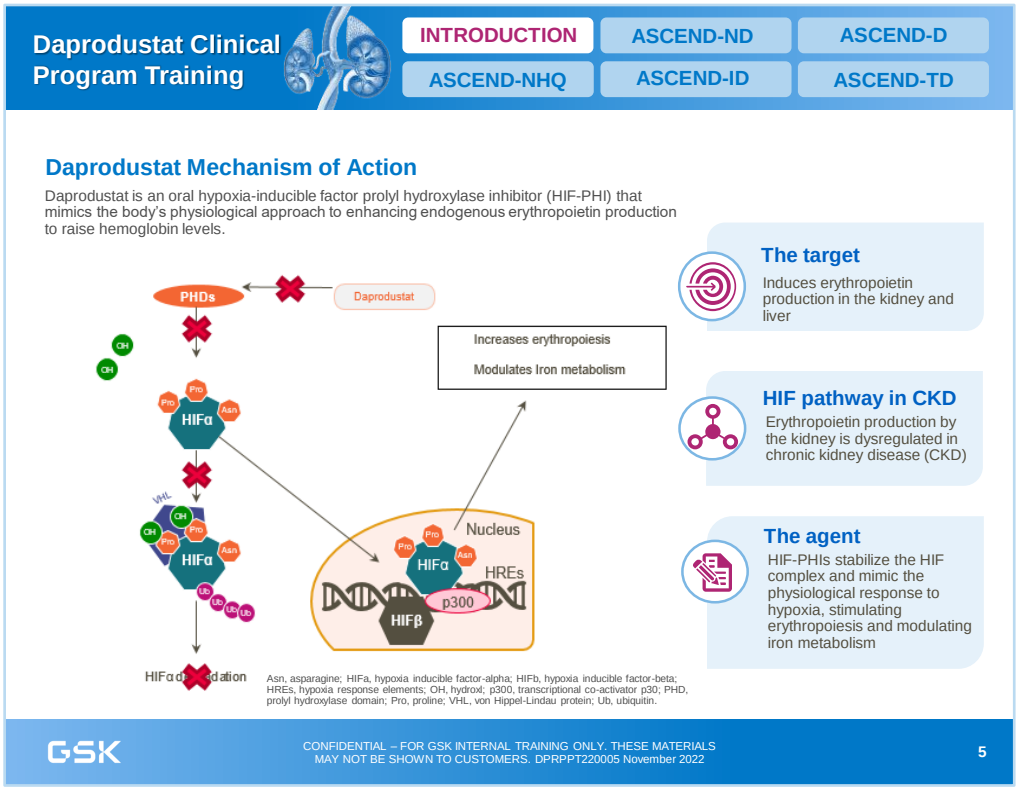
- *Today we will review the daprodustat mechanism of action and the key clinical trials that evaluated the safety and efficacy of daprodustat.*
- *Upon completion of this training, you will be able to:*
    - *Explain the mechanism of action of daprodustat*
    - *Provide an overview of the ASCEND program*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



Facilitator Notes

Say:

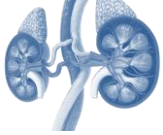
- *Let's begin with an overview of daprodustat and the ASCEND clinical trials.*
- *This section of the review will discuss the mechanism of action of daprodustat and introduce the 5 clinical trials that make up the ASCEND clinical program.*

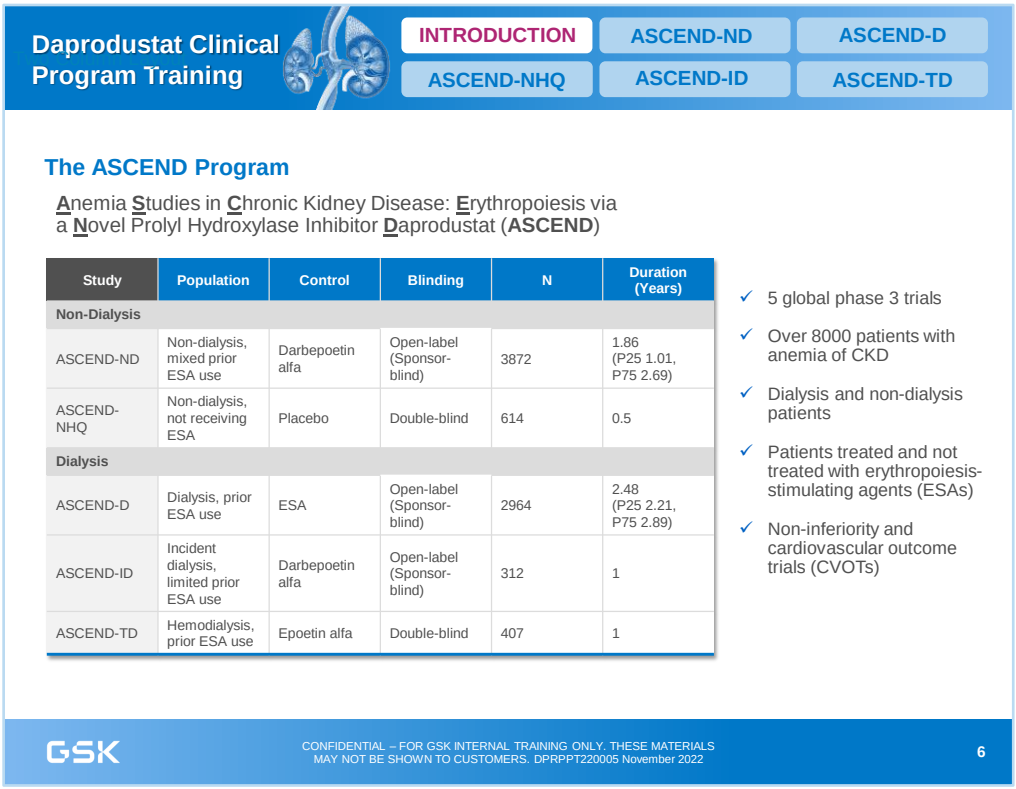


Facilitator Notes

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.*

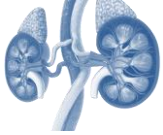


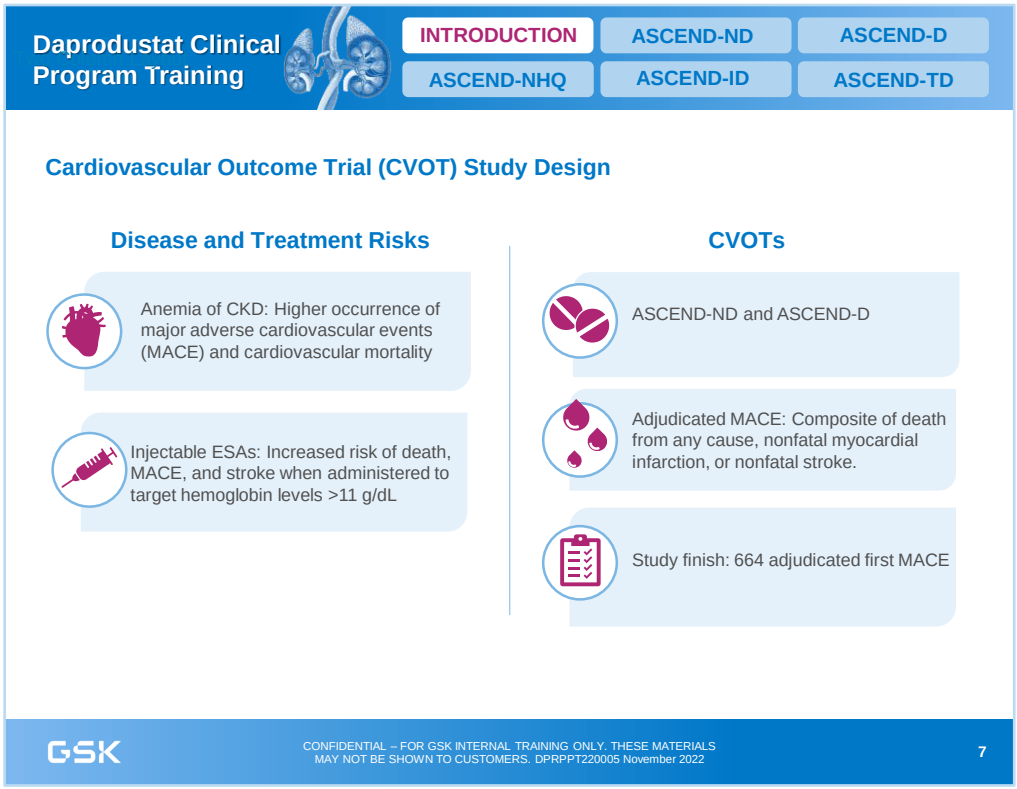


Facilitator Notes

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.*

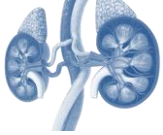




Facilitator Notes

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.*



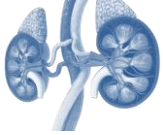
ASCEND Trials Baseline Characteristics

	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=155)	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)

Facilitator Notes

Say:

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



Dialysis Trials: Patient Characteristics[a]

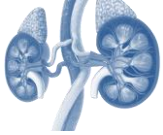
	ASCEND-D		ASCEND-ID		ASCEND-TD[b]	
	Daprodustat n=1487	ESA n=1477	Daprodustat n=157	Darbepoetin alfa n=155	Daprodustat n=270	Epoetin alfa n=137
Dialysis type at randomization, %						
Hemodialysis	89	89	80	81	100	100
Peritoneal dialysis	11	11	20	19	0	0
Hemoglobin, g/dL	10.3[c]	10.4[c]	9.5[c]	9.5[c]	10.5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

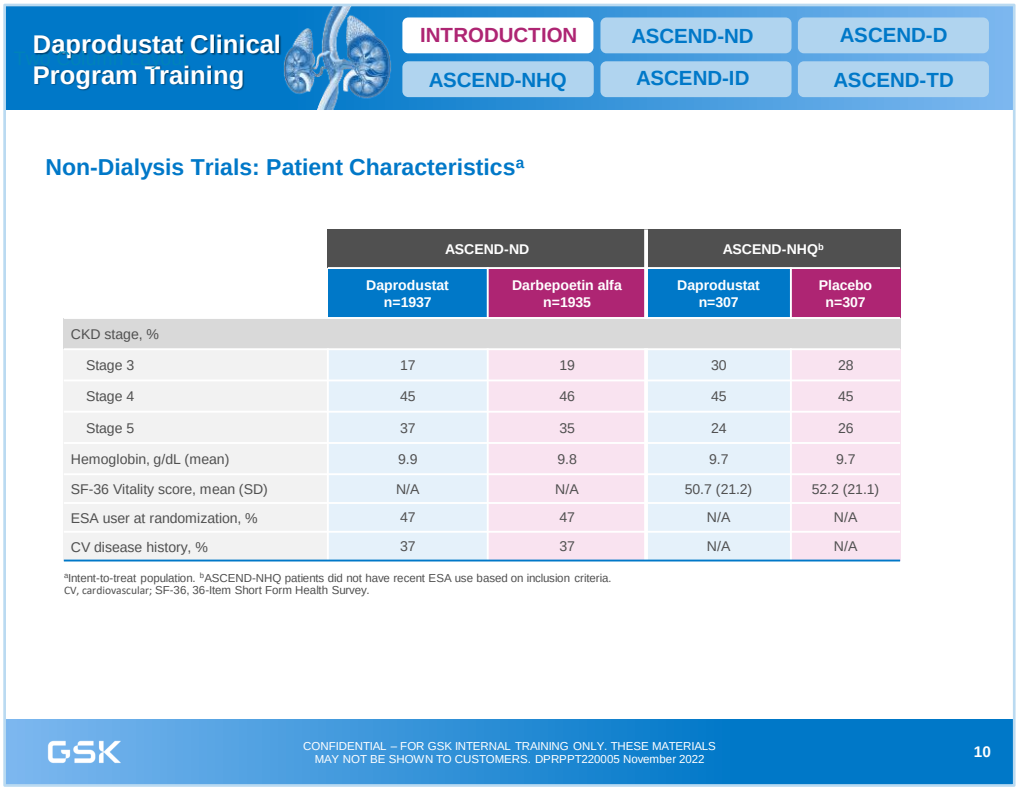
[a]Intent-to-treat population. [b]Based on inclusion criteria, all patients in ASCEND-TD were on HD. [c]Mean value. [d]Median value with interquartile range.

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.*

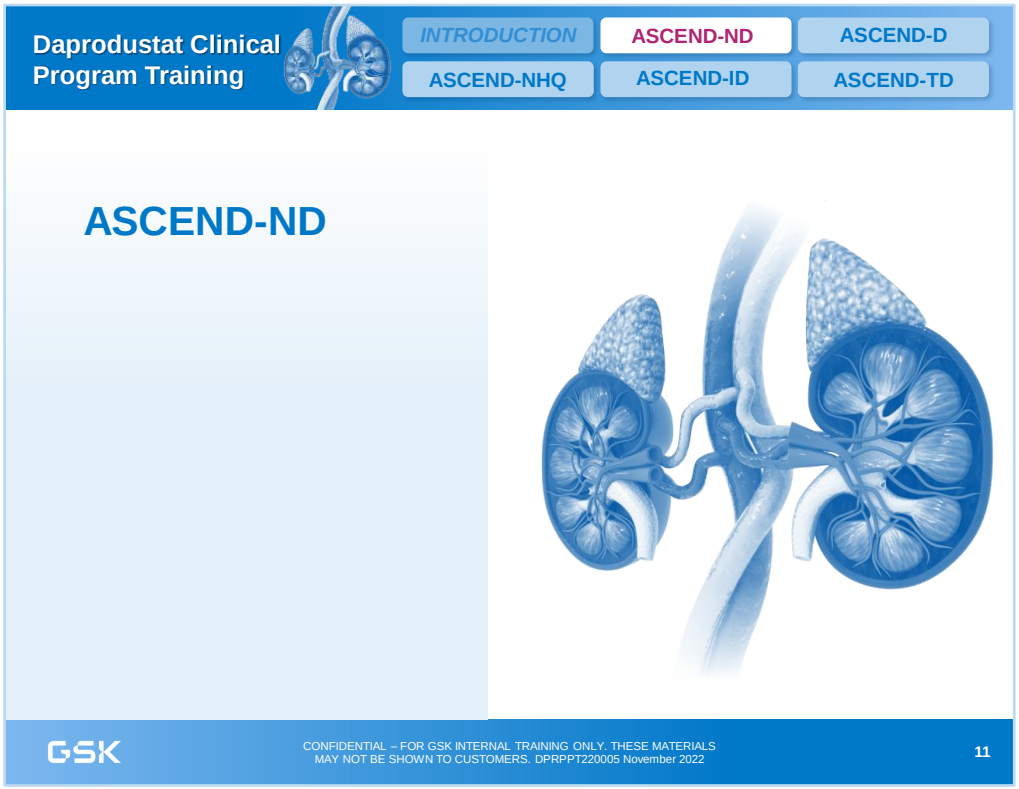




Facilitator Notes

Say:

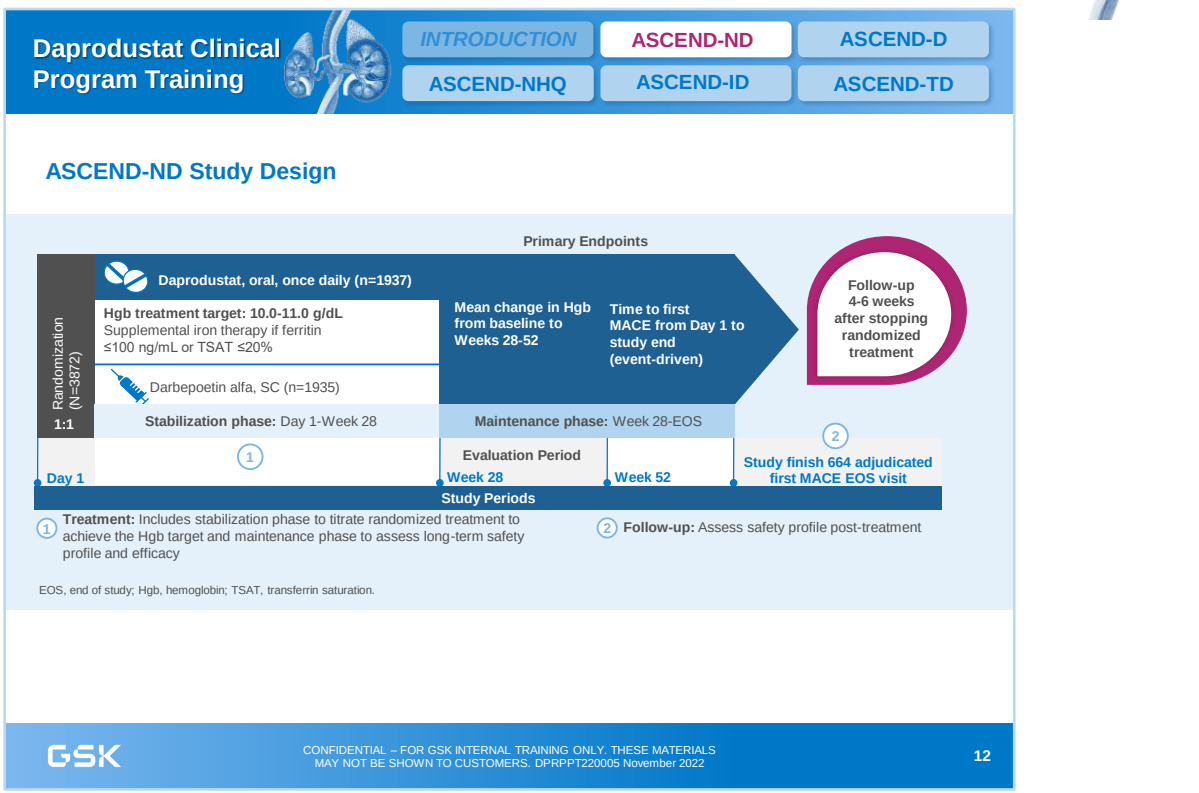
- *This table reviews the patient characteristics in the ASCEND trials that enrolled non-dialysis patients.*
- *ASCEND-ND was a cardiovascular outcome trial, which is why cardiovascular disease history is important.*
- *Patients in the ASCEND-ND trials tended to have higher stage CKD than those in ASCEND-NHQ.*
- *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.*



Facilitator Notes

Say:

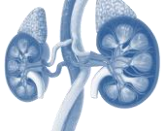
- *Now that we have reviewed the ASCEND program as a whole, let's take a look at the study design and outcomes of each study individually.*
- *In this section, we will focus on the ASCEND-ND study.*

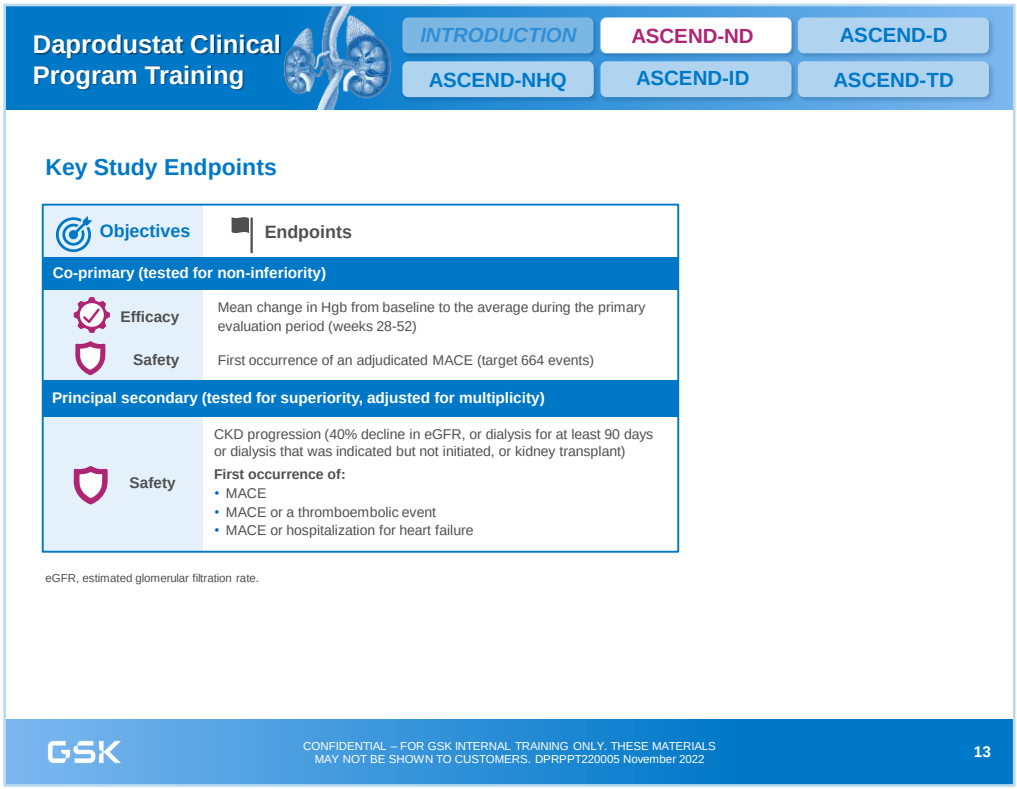


Facilitator Notes

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 ≤100 ng/mL or TSAT was ≤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.*

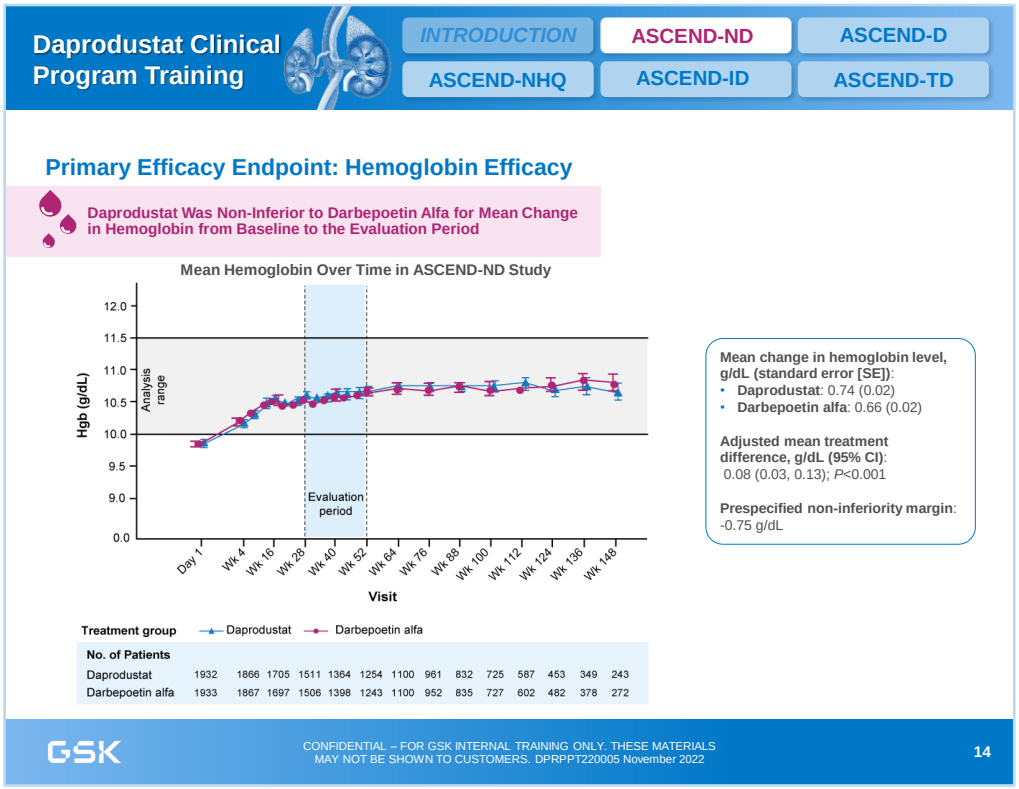




Facilitator Notes

Say:

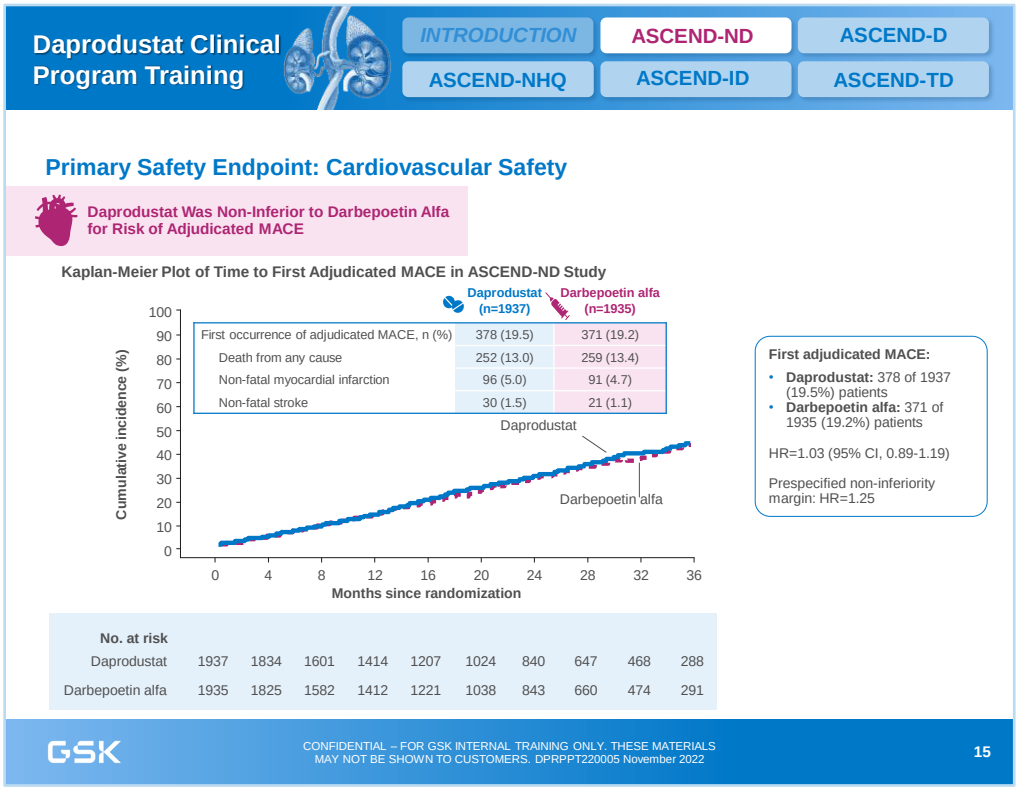
- *ASCEND-ND evaluated daprodustat versus darbepoetin alfa for co-primary non-inferiority endpoints and principal secondary superiority endpoints.*
- *The co-primary endpoints, tested for non-inferiority, were:*
  - *Mean change in hemoglobin from baseline to the average during the primary evaluation 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*



Facilitator Notes

Say:

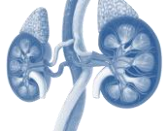
- *In ASCEND-ND, daprodustat met the primary efficacy endpoint, showing non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28 to 52.*
- *In this graph, the hemoglobin target range for dose changes was 10.0 to 11.0 g/dL. The horizontal lines represent the hemoglobin 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.*



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.*



Principal Secondary Endpoints

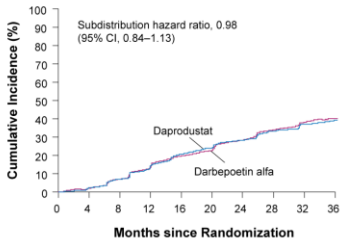
Daprodustat Was Not Superior to Darbepoetin Alfa for First Occurrence of MACE, the First Occurrence of MACE or a Thromboembolic Event, and the First Occurrence of MACE or Hospitalization for Heart Failure

Cardiovascular Safety

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)

Daprodustat Was Not Superior to Darbepoetin Alfa for Progression of CKD

Progression of CKD



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

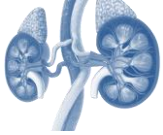
Progression of CKD:
- **Daprodustat**: 28.1% of patients
- **Darbepoetin alfa**: 28.4% of patients

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

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.*



Safety: Adverse Events

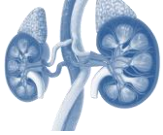
AEs, SAEs, and AEs occurring in ≥10% of patients were **generally similar between the daprodustat and darbepoetin alfa groups**.

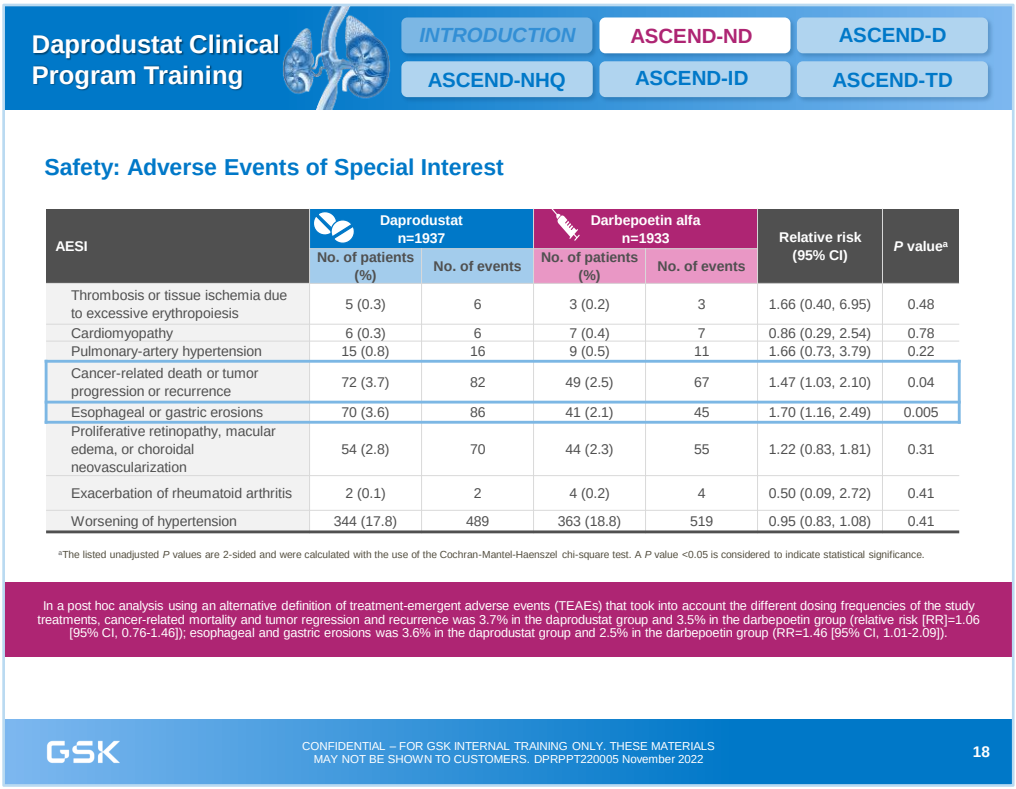
AE	Daprodustat n=1937	Darbepoetin alfa n=1933
	No. of patients (%)	No. of patients (%)
Any AE	1545 (79.8)	1487 (76.9)
Any SAE	850 (43.9)	703 (36.4)
AEs occurring in ≥10% of patients		
Hypertension	257 (13)	272 (14)
Urinary tract infection	187 (10)	179 (9)
Peripheral edema	199 (10)	166 (9)

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.*

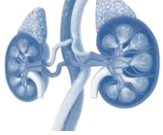


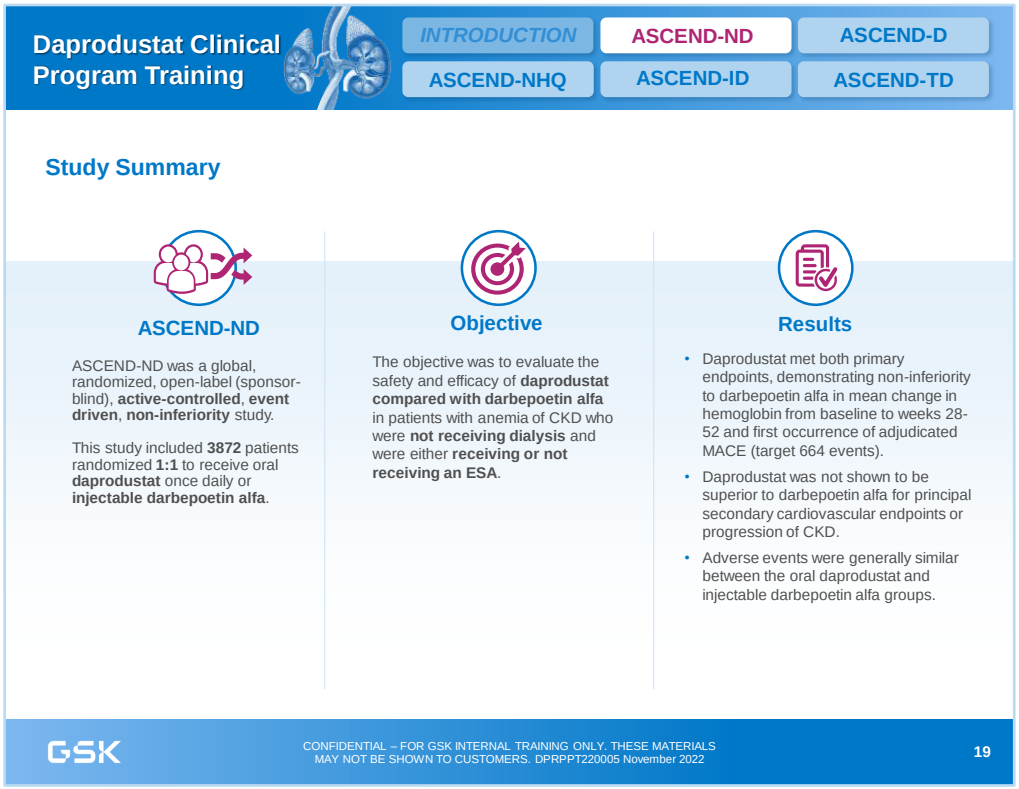


Facilitator Notes

Say:

- *Prespecified adverse events of special interest were generally consistent across the daprodustat and darbepoetin 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 darbepoetin 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 darbepoetin group.*

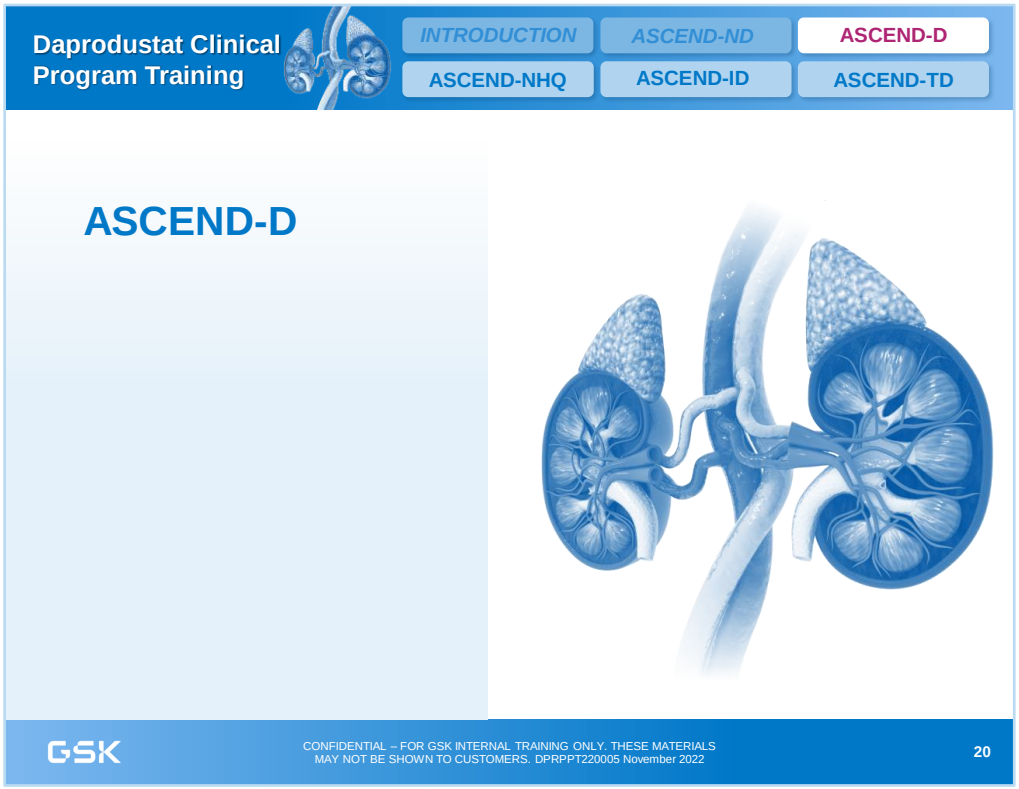




Facilitator Notes

Say:

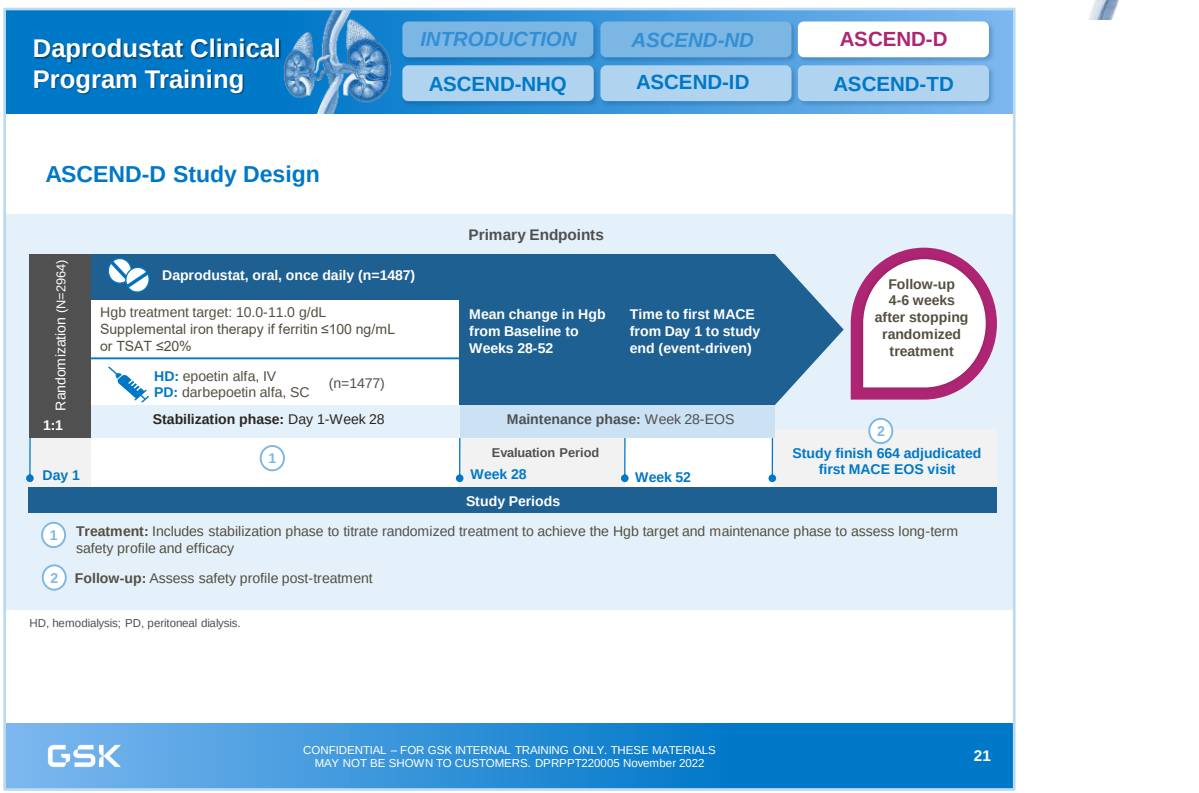
- *ASCEND-ND was a global, randomized, open-label (sponsor-blind), active-controlled, event-driven, non-inferiority study.*
- *This study included 3872 patients randomized 1:1 to receive oral daprodustat once daily or injectable darbepoetin alfa.*
- *The objective was to evaluate the safety and efficacy 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.*



Facilitator Notes

Say:

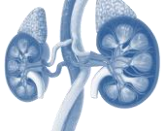
- *Now let's discuss the ASCEND-D study.*

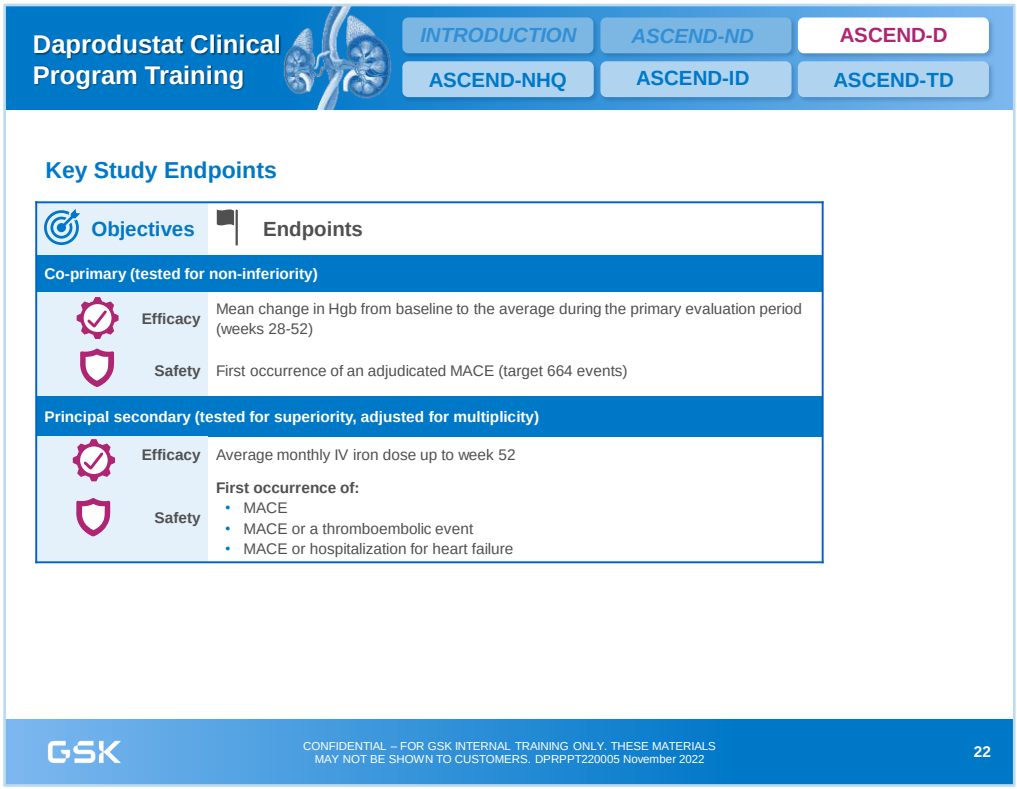


Facilitator Notes

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.*

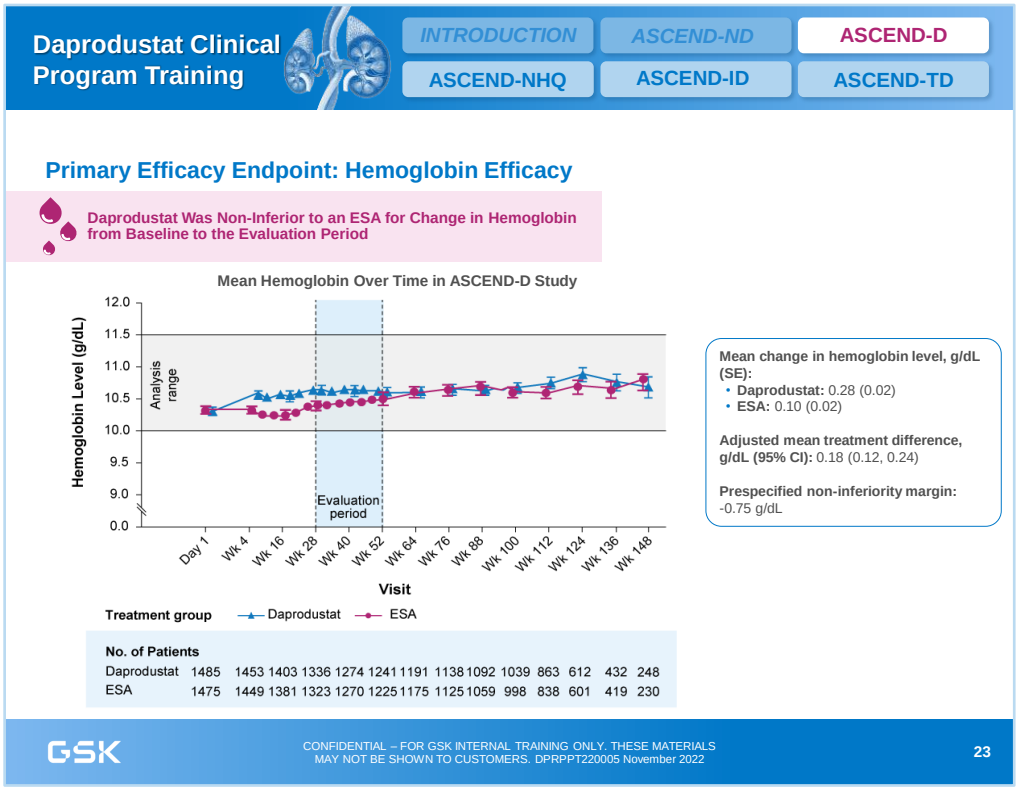




Facilitator Notes

Say:

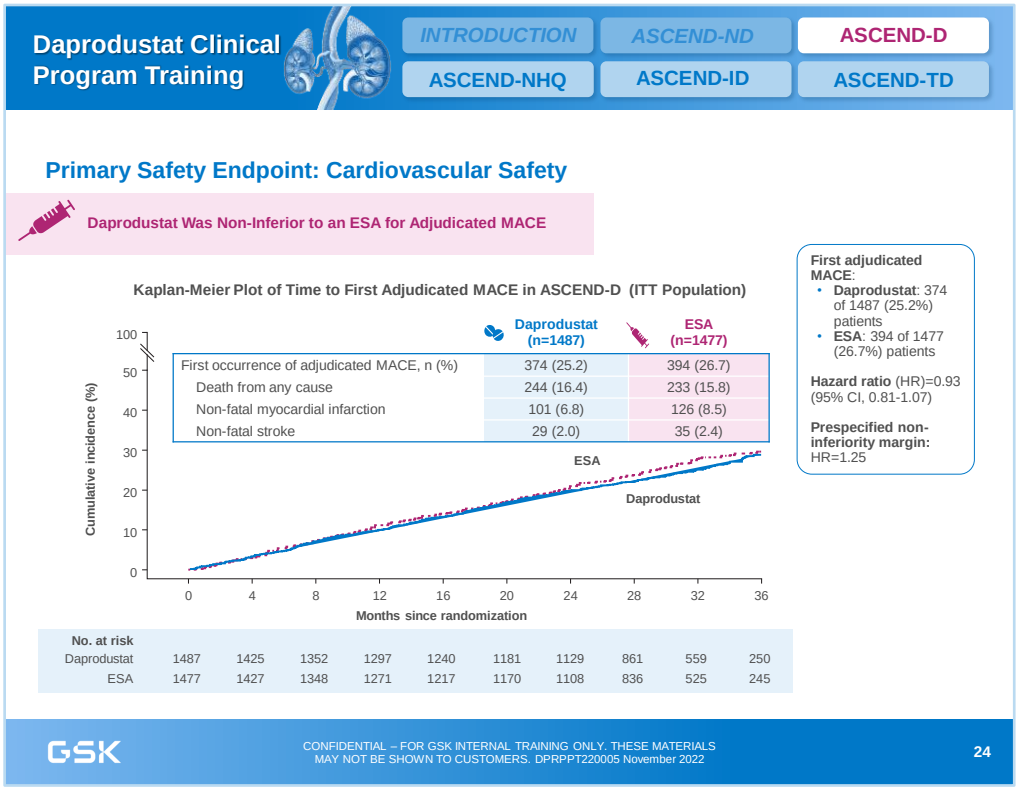
- *ASCEND-D evaluated daprodustat versus epoetin alfa or darbepoetin alfa for co-primary non-inferiority endpoints and principal secondary superiority endpoints.*
- *The co-primary endpoints, tested for non-inferiority, were:*
  - *Mean change in hemoglobin from baseline to the average during the primary 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*



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.*



Facilitator Notes

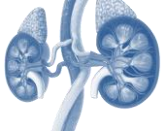
Say:

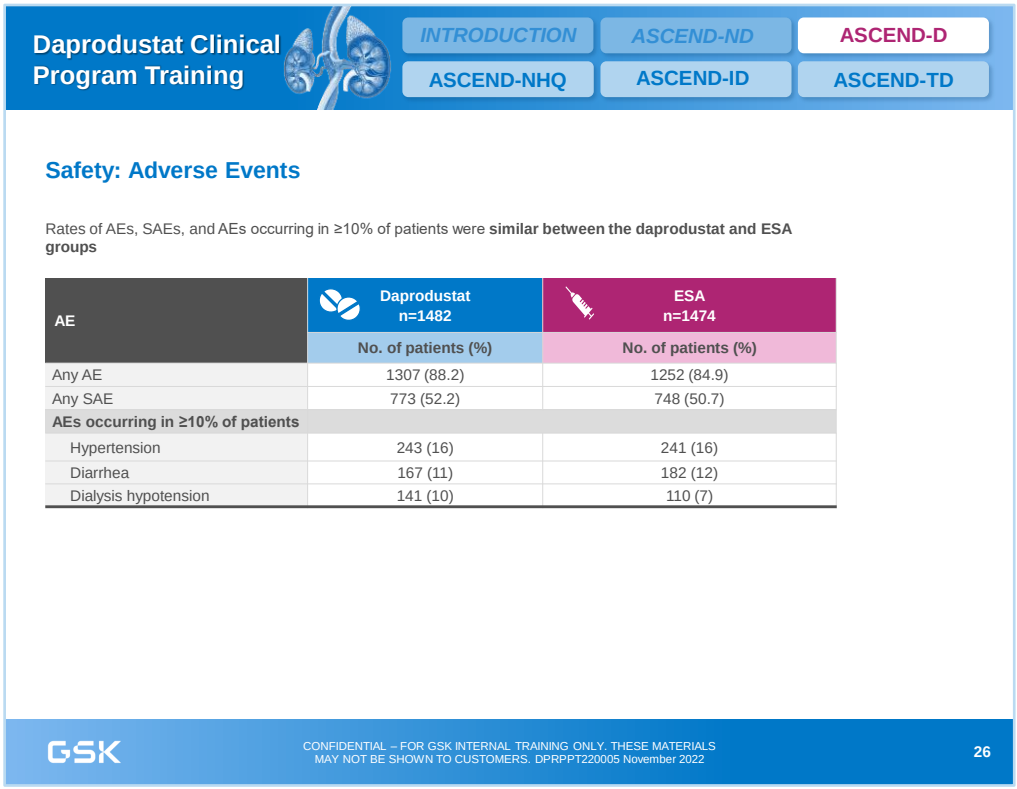
- *Daprodustat also met the primary safety endpoint, showing non-inferiority to an ESA for risk of adjudicated MACE.*
- *A first adjudicated MACE occurred in 25.2% of patients in the daprodustat group and 26.7% of patients in the ESA group.*
- *The hazard ratio for this difference was 0.93.*
- *Non-inferiority 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.*

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.*

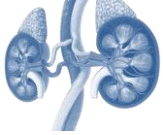




Facilitator Notes

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.*



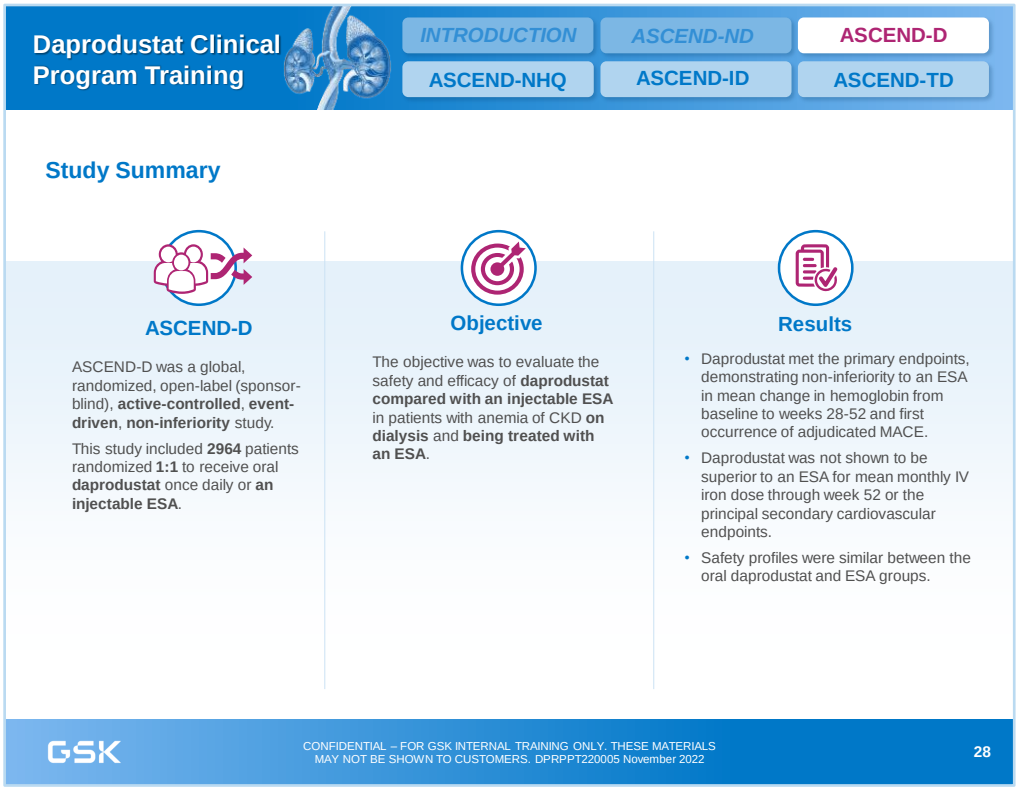
Safety: Adverse Events of Special Interest

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)

Facilitator Notes

Say:

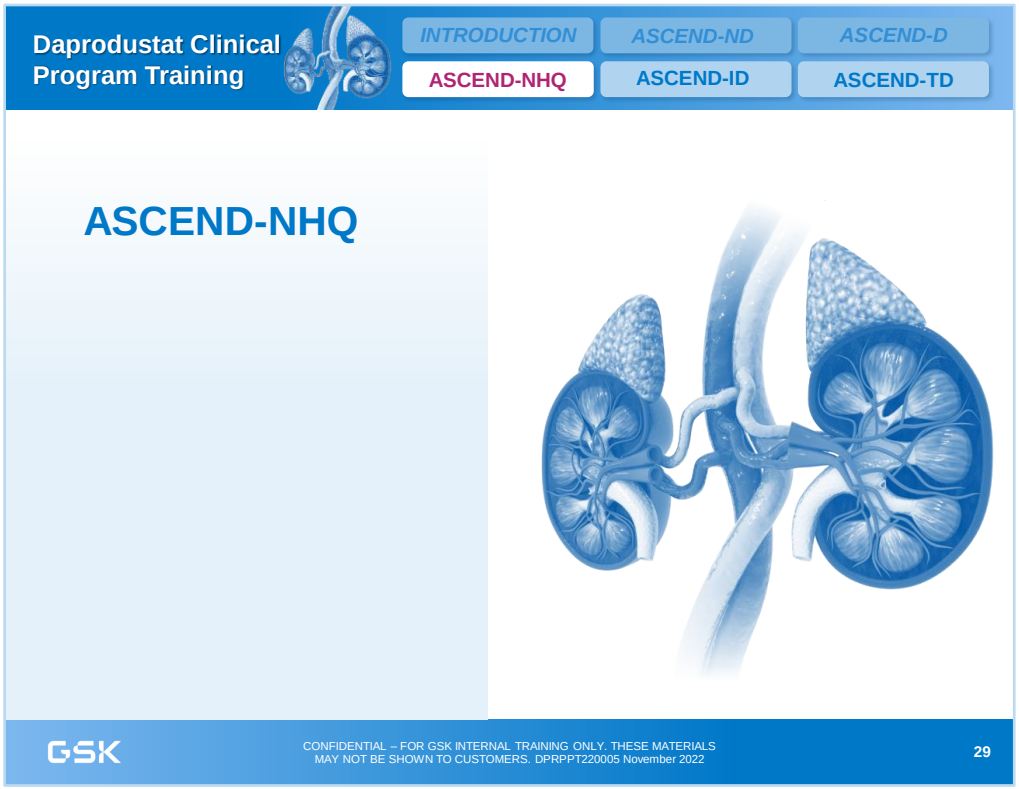
- *Prespecified adverse events of special interest were found to be similar between the daprodustat and ESA groups.*



Facilitator Notes

Say:

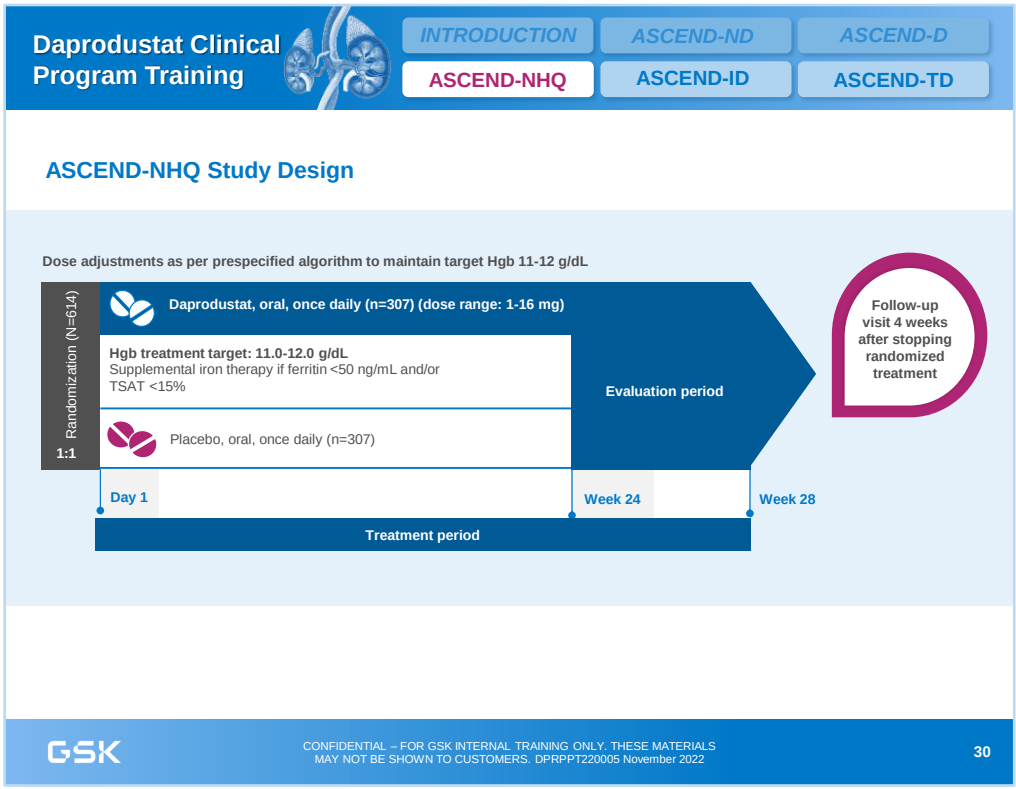
- *ASCEND-D was a global, randomized, open-label (sponsor-blind), active-controlled, event-driven, non-inferiority study.*
- *This study included 2964 patients randomized 1:1 to receive oral daprodustat once daily or an injectable ESA.*
- *The objective was to evaluate the safety and efficacy of daprodustat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



Facilitator Notes

Say:

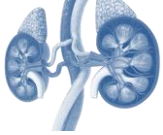
- *In this section, we'll review the study design and outcomes of ASCEND-NHQ.*

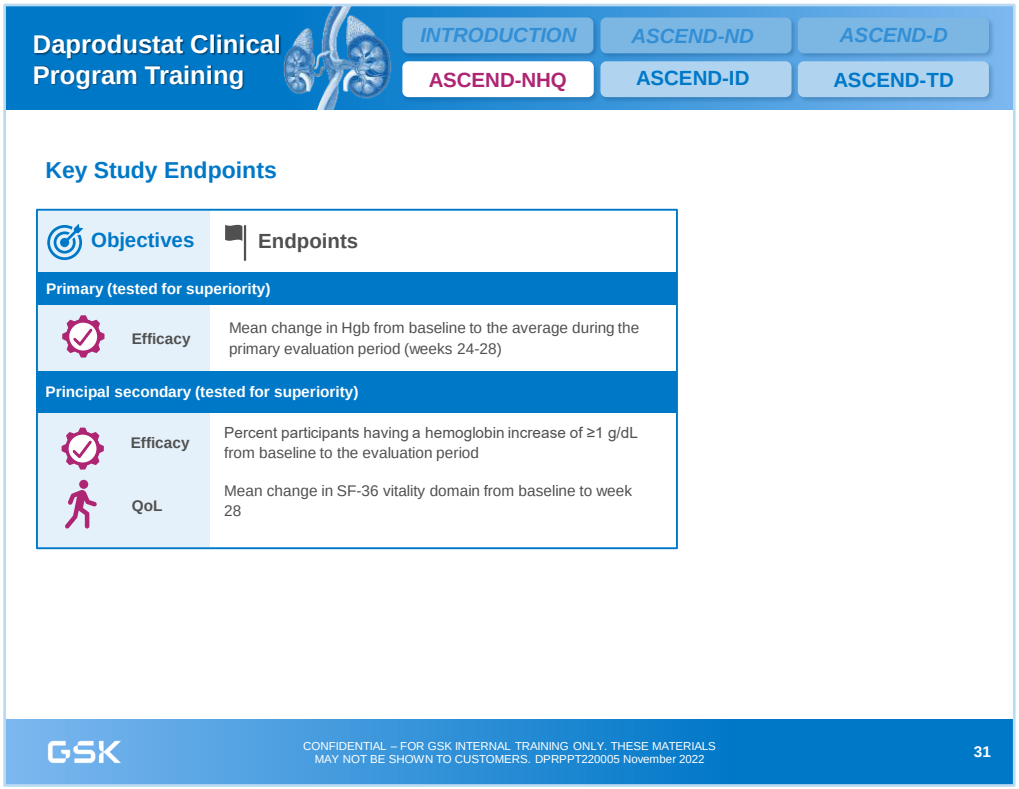


Facilitator Notes

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.*

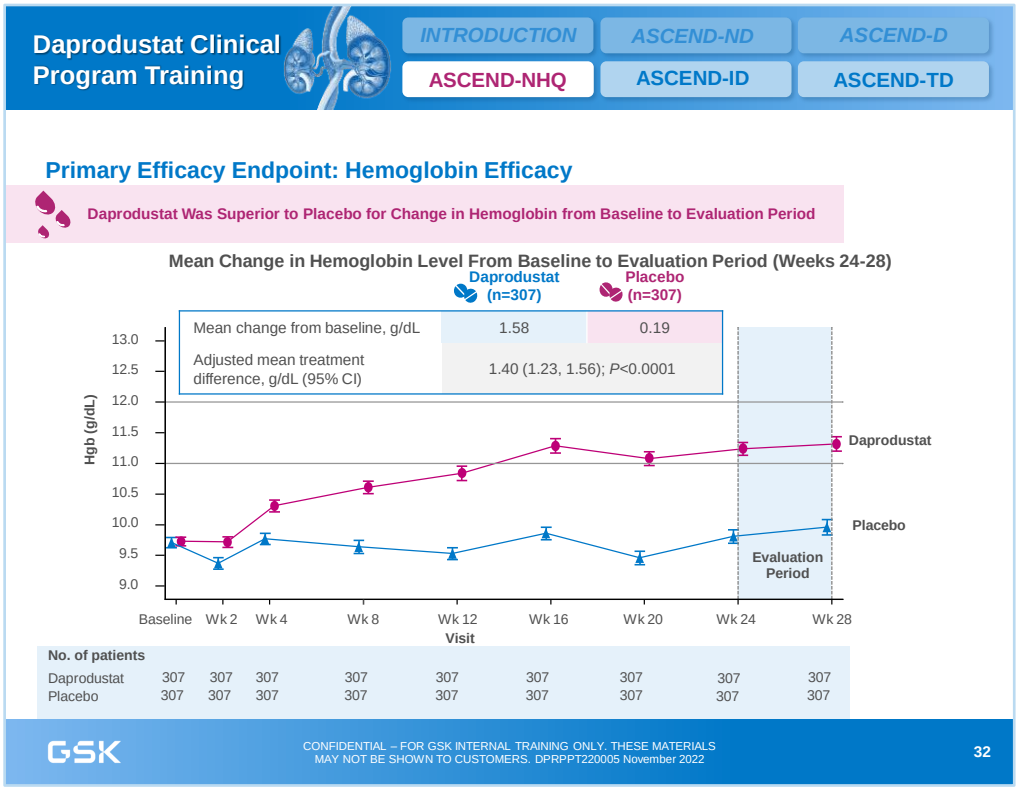




Facilitator Notes

Say:

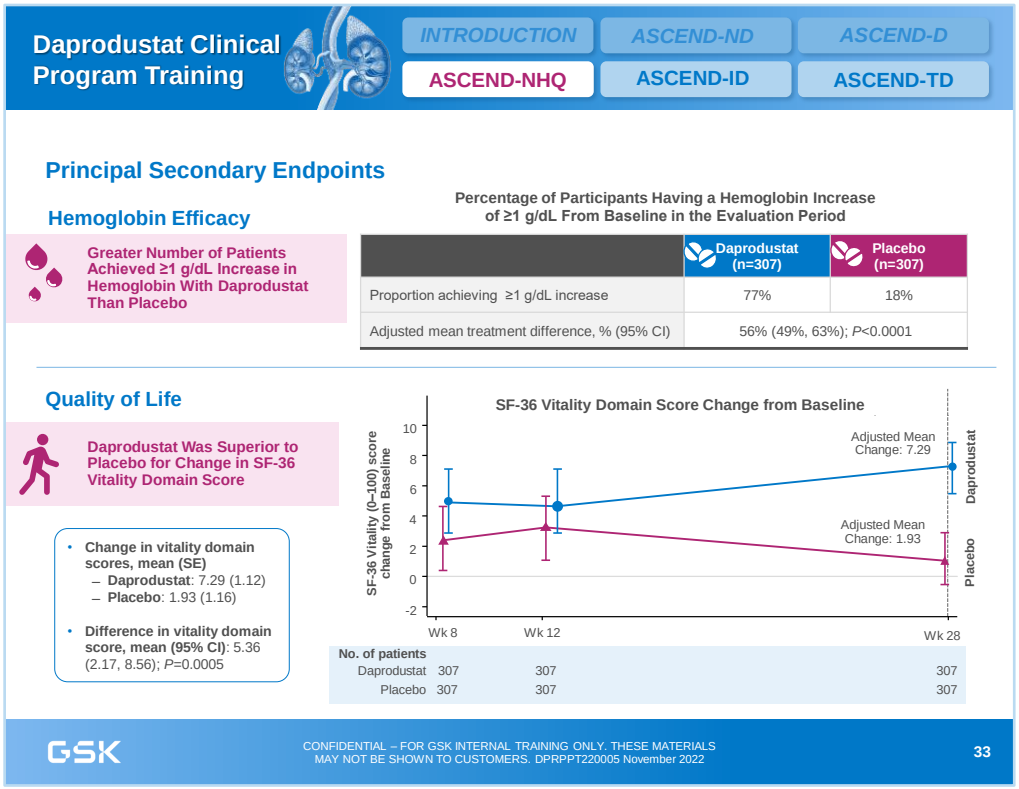
- *ASCEND-NHQ evaluated daprodustat versus placebo for superiority in a primary endpoint and principal secondary endpoints.*
- *The primary endpoint, tested for superiority, was mean change in hemoglobin from baseline to the average during the primary evaluation period, weeks 24 to 28.*
- *The principal 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*



Facilitator Notes

Say:

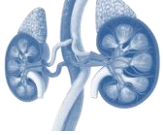
- *In ASCEND-NHQ, daprodustat met the primary endpoint, showing superiority to placebo for mean change in hemoglobin level at weeks 24 to 28.*
- *The mean change in hemoglobin from baseline to the evaluation period was 1.58 g/dL in the daprodustat group and 0.19 g/dL in the placebo group.*
- *This was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

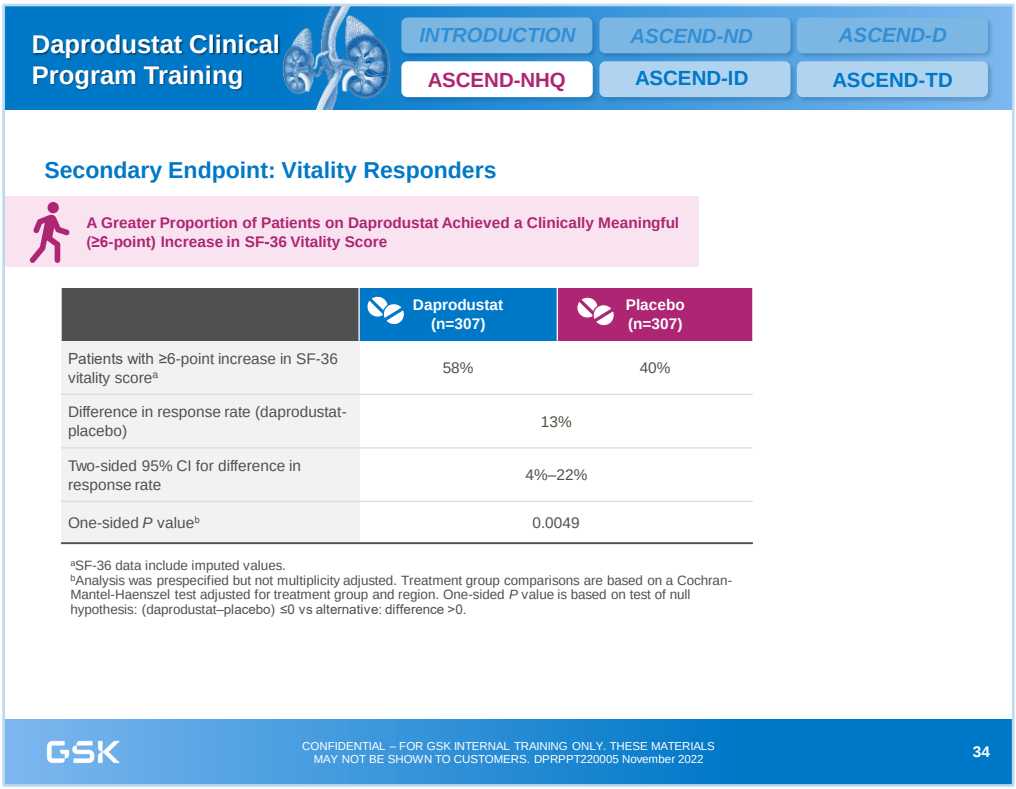


Facilitator Notes

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.*

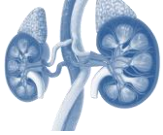




Facilitator Notes

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 ≥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.*



Safety: Adverse Events

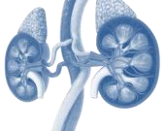
AEs, SAEs, and AEs occurring in ≥5% of patients were **similar between the daprodustat and placebo groups**.

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)
AEs occurring in ≥5% of patients		
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)

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.*



Safety: Adverse Events of Special Interest

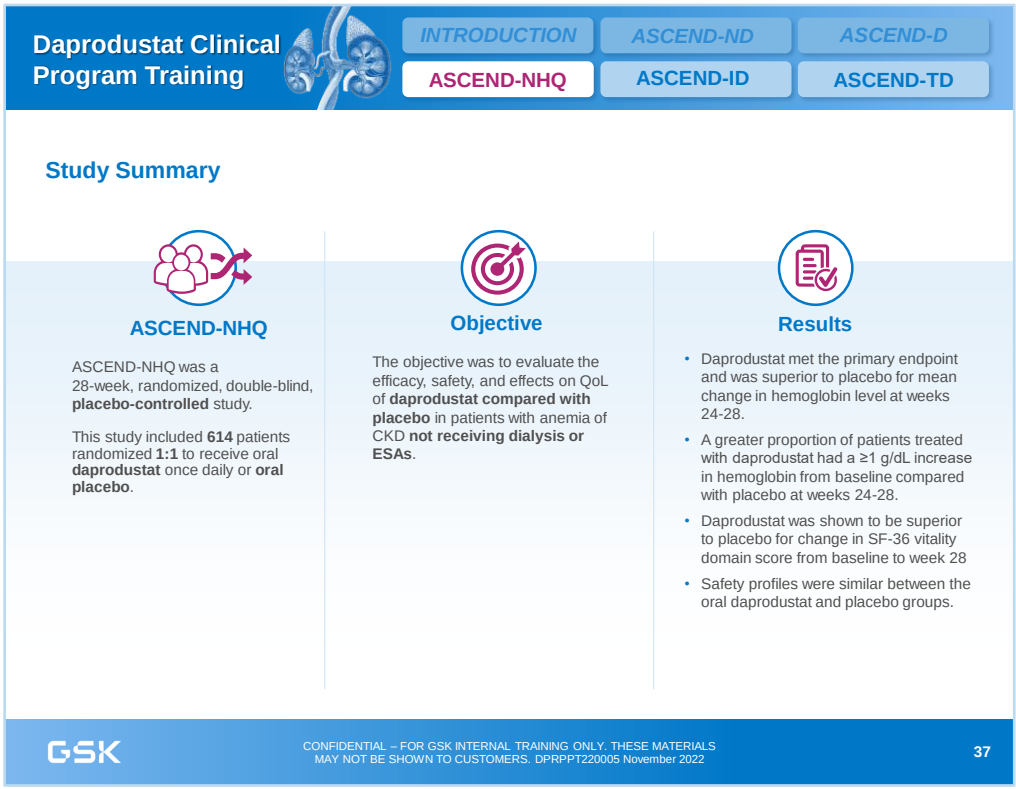
AESI	Daprodustat n=308	Placebo n=306
	No. of patients (%)	No. of patients (%)
Death, myocardial infarction, stroke, heart failure, PE, DVT, thromboembolic events, thrombosis of vascular access	26 (8)	23 (8)
Pulmonary-artery hypertension	3 (<1)	0
Cancer-related death or tumor progression or recurrence	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.

Facilitator Notes

Say:

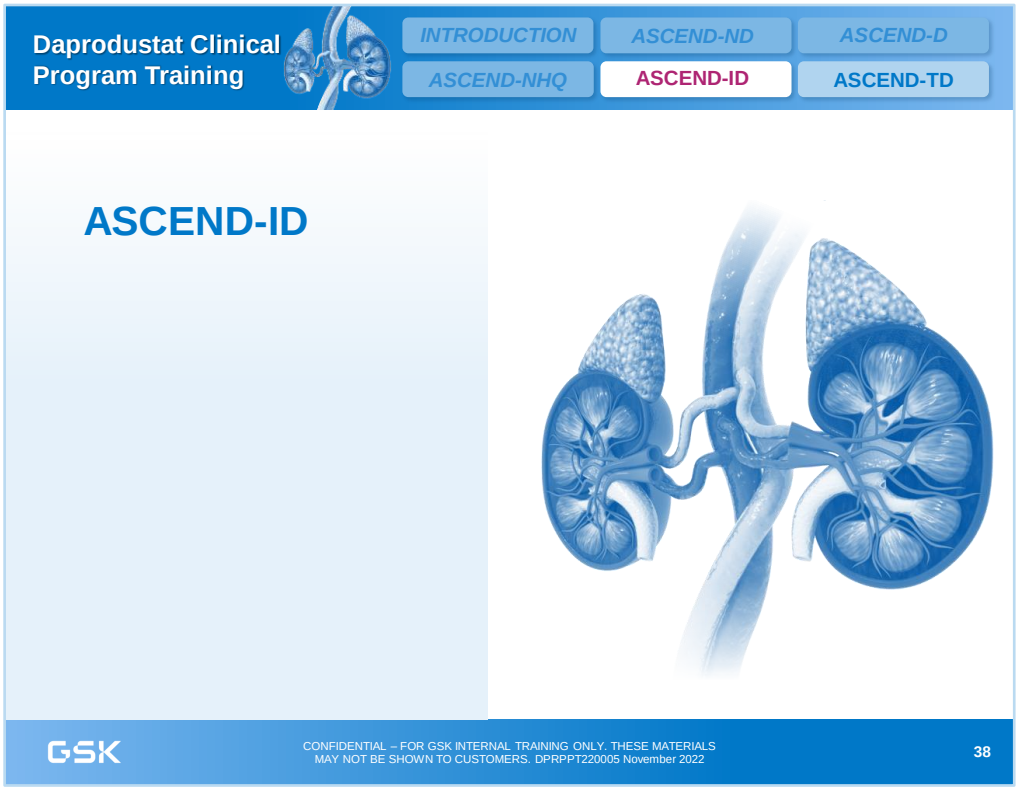
- *Prespecified adverse events of special interest were consistent across the daprodustat and placebo treatment arms.*



Facilitator Notes

Say:

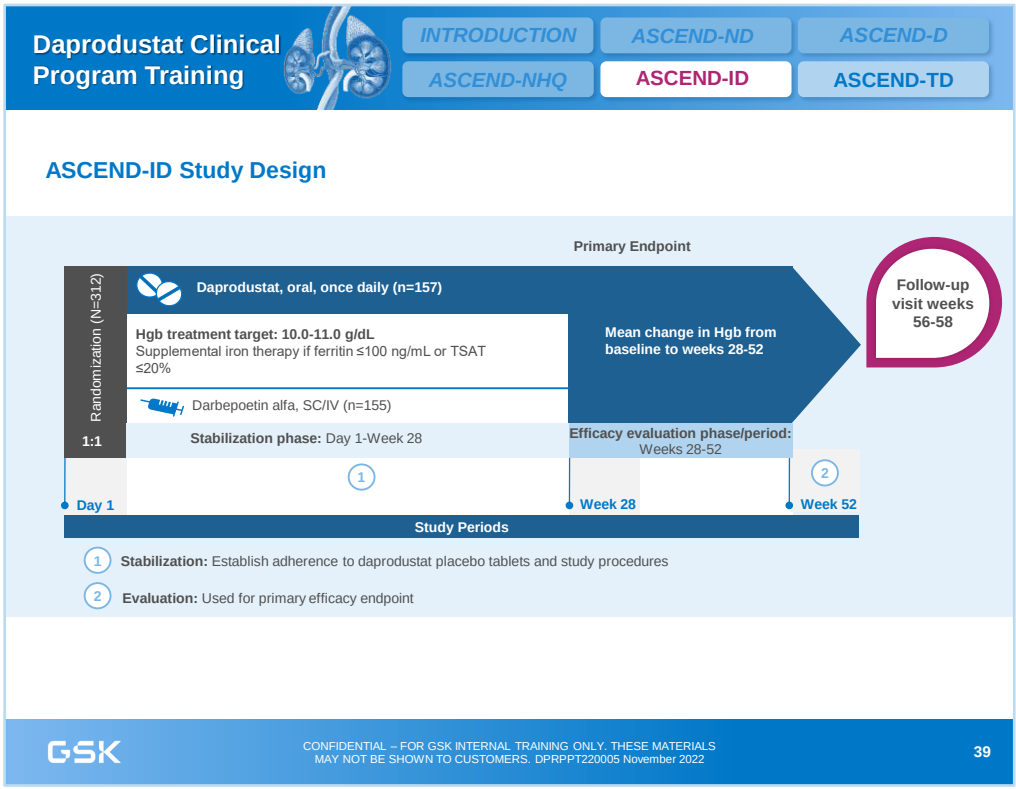
- *ASCEND-NHQ was a 28-week, randomized, double-blind, placebo-controlled study.*
- *This study included 614 patients randomized 1:1 to receive oral daprodustat once daily or oral placebo.*
- *The objective was to evaluate the efficacy, safety, and effects on quality of life of daprodustat compared with 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 ≥6-point increase in SF-36 vitality score compared with placebo.*
- *Safety profiles were similar between the oral daprodustat and placebo groups.*



Facilitator Notes

Say:

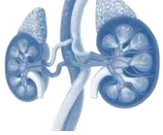
- *Now we will review the ASCEND-ID study.*
- *ID is short for incident dialysis.*
- *While the ASCEND-D trial enrolled patients on dialysis who were established and physiologically stable, the ASCEND-ID trial enrolled patients receiving incident dialysis, which is typically defined as dialysis initiated 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.*

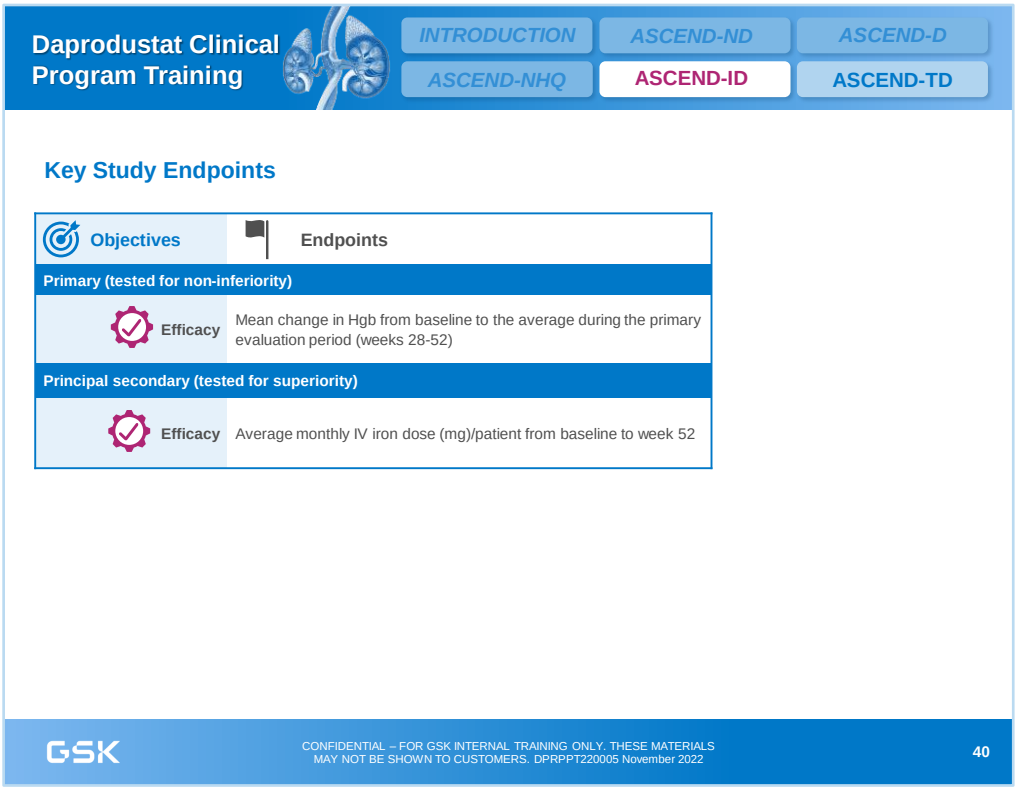


Facilitator Notes

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.*

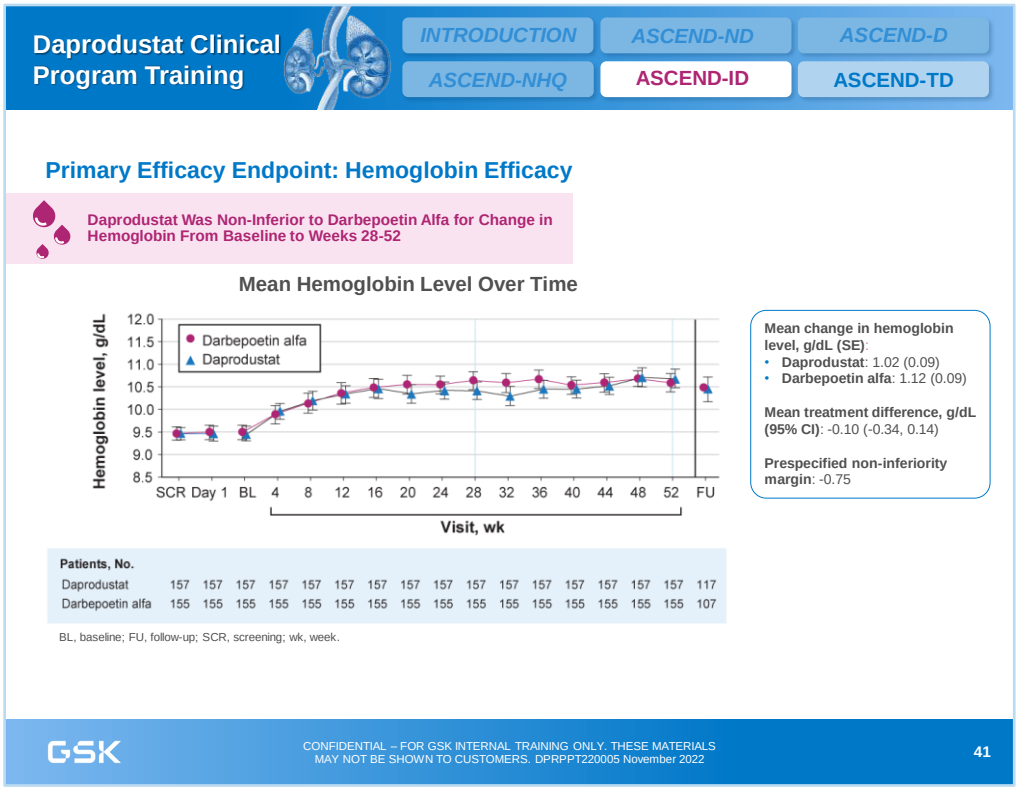




Facilitator Notes

Say:

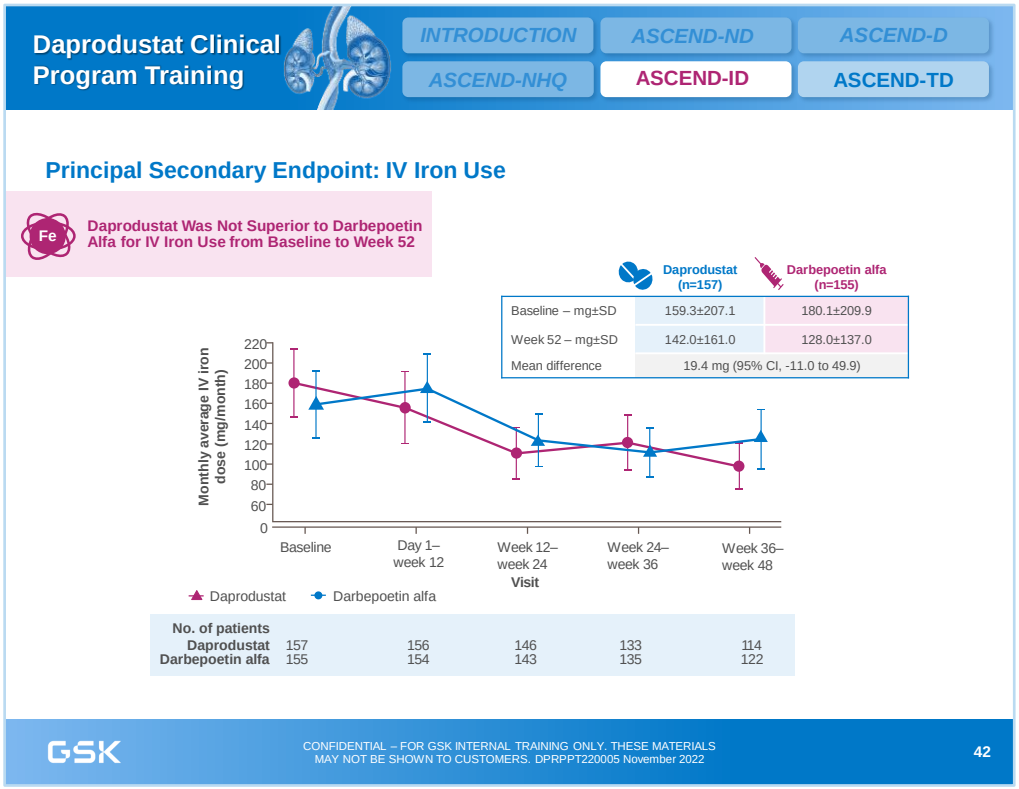
- *ASCEND-ID evaluated daprodustat versus darbepoetin alfa for 1 primary non-inferiority endpoint and 1 principal secondary superiority endpoint.*
- *The primary endpoint, tested for non-inferiority, was mean change in hemoglobin from baseline to the average during the primary evaluation period (weeks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



Facilitator Notes

Say:

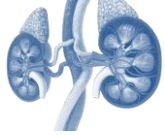
- *In ASCEND-ID, daprodustat met the primary efficacy endpoint, showing non-inferiority to darbepoetin alfa in mean change in hemoglobin from baseline to weeks 28 to 52.*
- *The mean change in hemoglobin level was 1.02 g/dL for the daprodustat group and 1.12 g/dL for the darbepoetin alfa group.*
- *The 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.*

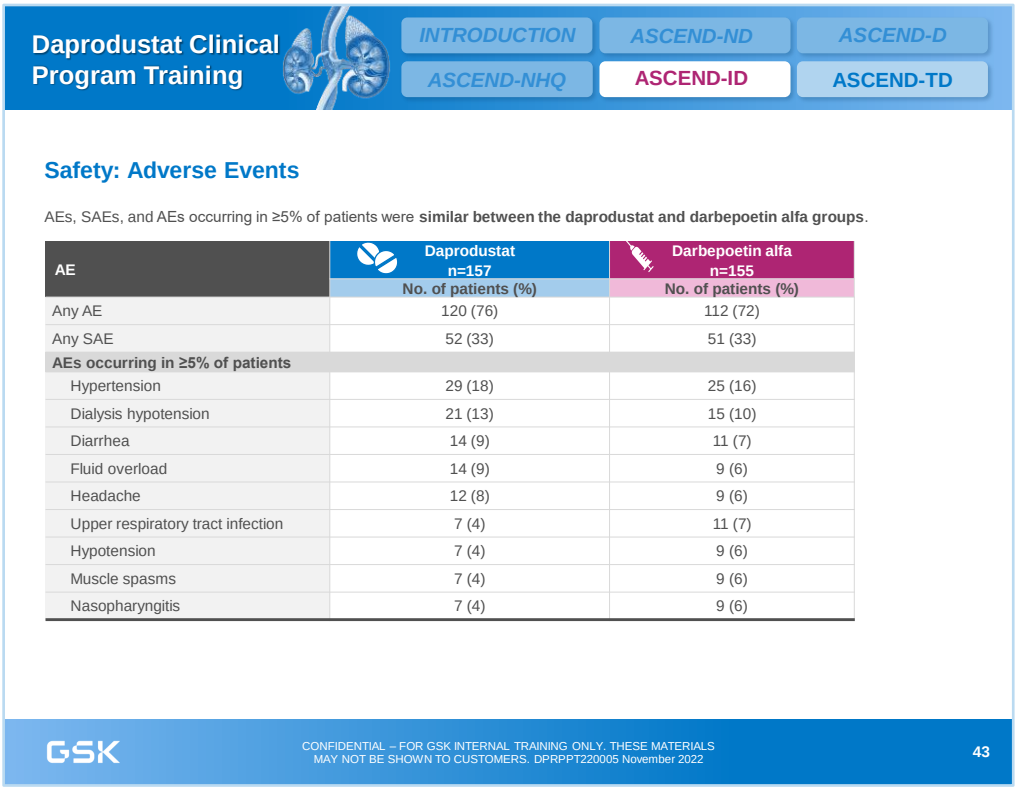


Facilitator Notes

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.*

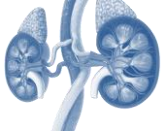




Facilitator Notes

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.*



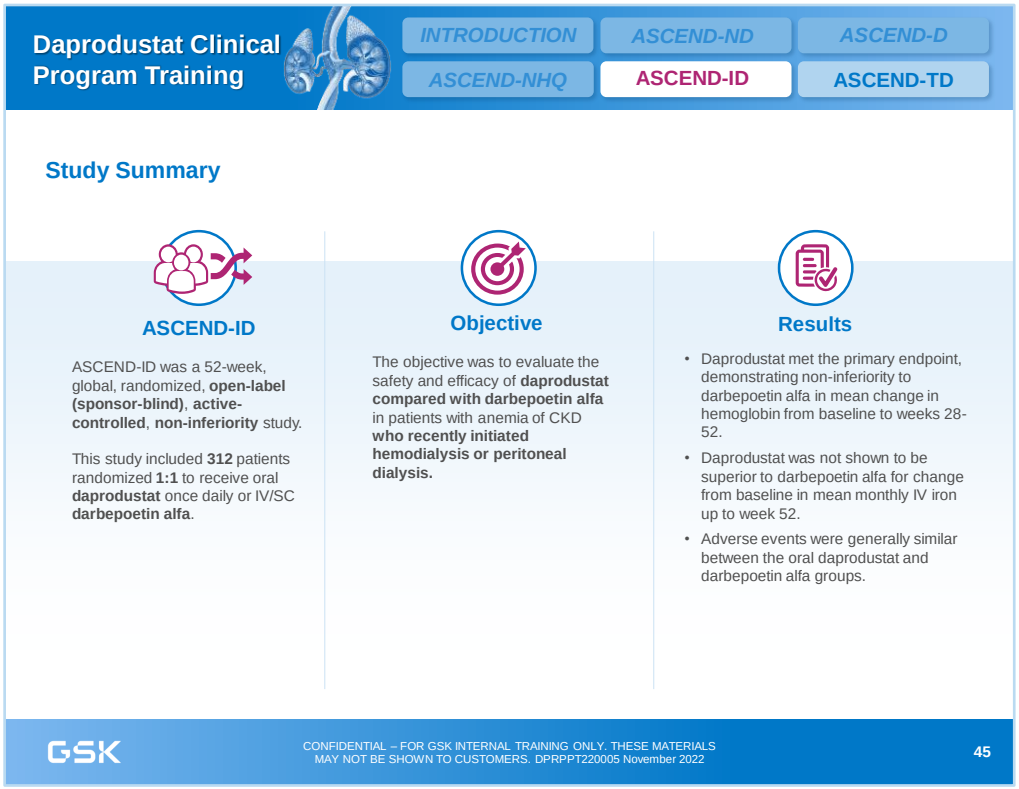
Safety: Adverse Events of Special Interest

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

Facilitator Notes

Say:

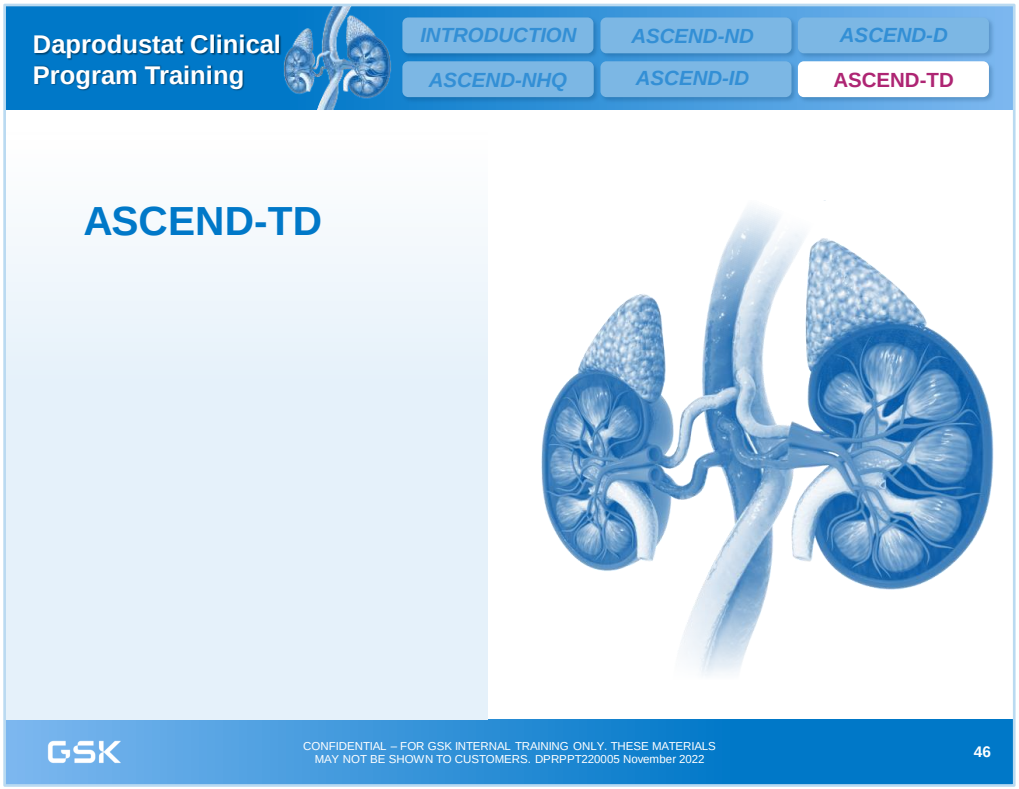
- *Prespecified adverse events of special interest were consistent across the daprodustat and darbepoetin alfa treatment arms, except for worsening of hypertension, which was higher in the daprodustat arm.*
- *Note that although there was a higher percentage of worsening hypertension in the daprodustat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



Facilitator Notes

Say:

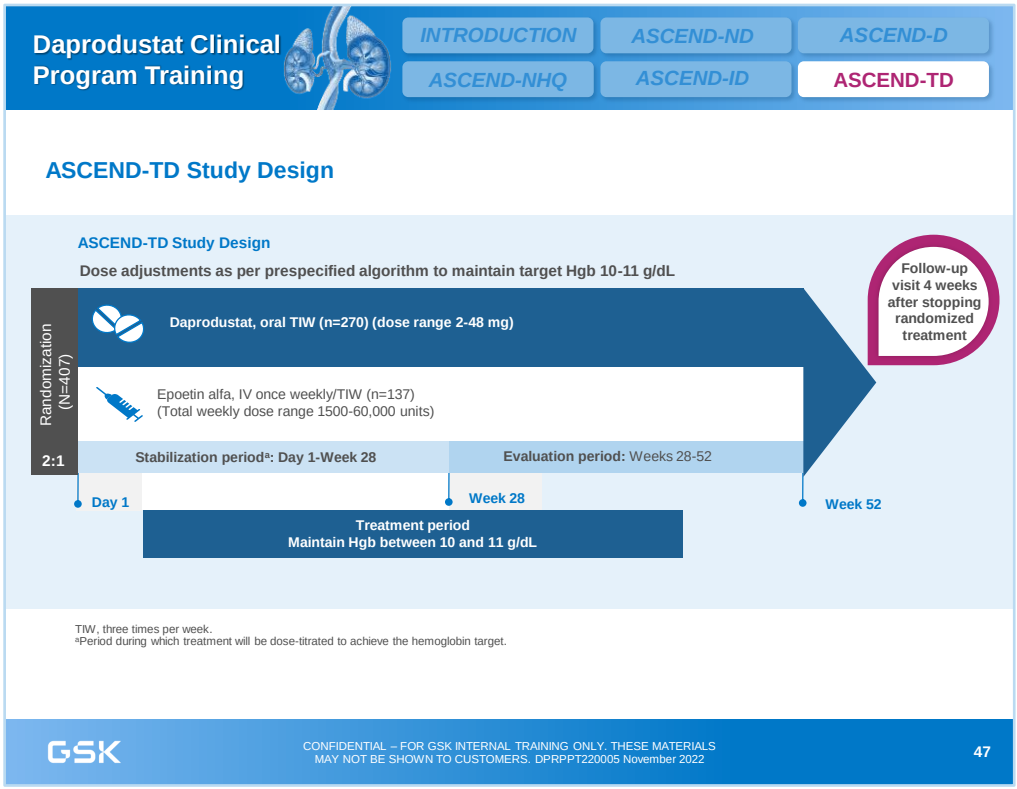
- *ASCEND-ID was a 52-week, global, randomized, open-label (sponsor-blind), active-controlled, non-inferiority study.*
- *This study included 312 patients randomized 1:1 to receive oral daprodustat once daily or darbepoetin alfa intravenous or subcutaneous based on the type of dialysis the patient was 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.*



Facilitator Notes

Say:

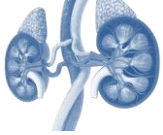
- *Lastly, let's look at the study design and outcomes of ASCEND-TD.*
- *The ASCEND-TD study is the only study in the ASCEND program where daprodustat was given 3 times per week.*
- *Remember that hemodialysis is usually given in a dialysis clinic 3 times per week, with short-acting ESAs, such as epoetin 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.*

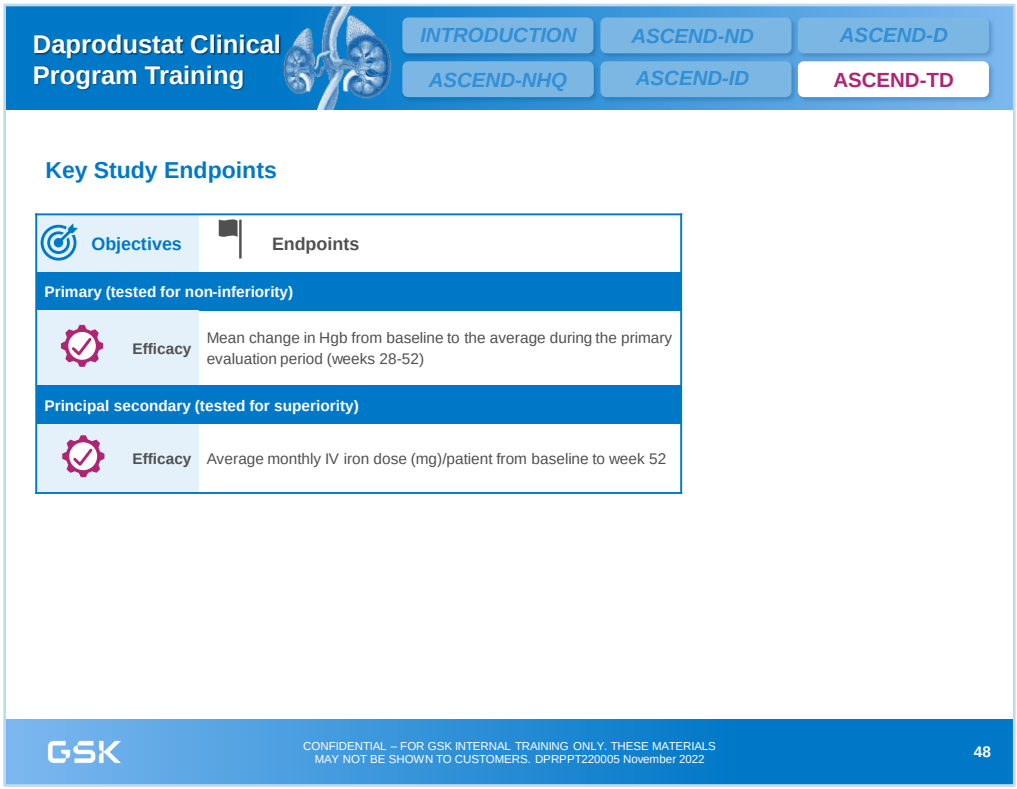


Facilitator Notes

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.*

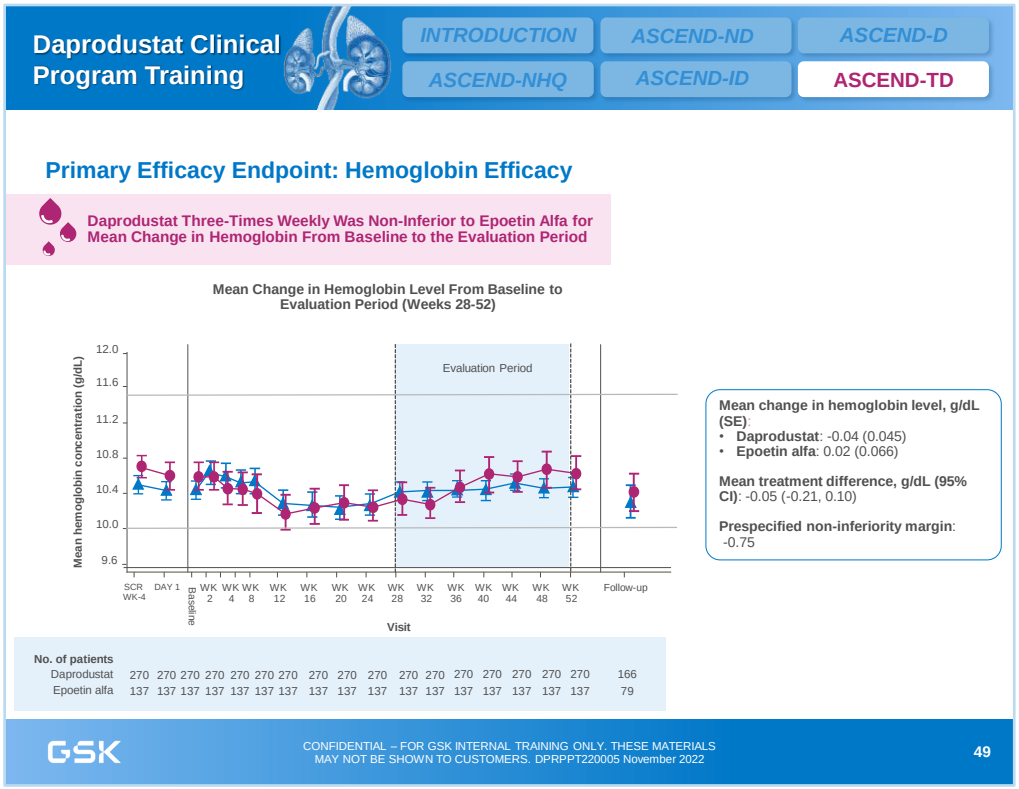




Facilitator Notes

Say:

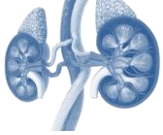
- *ASCEND-TD evaluated daprodustat versus epoetin alfa for 1 primary non-inferiority endpoint and 1 principal secondary superiority endpoint.*
- *The primary endpoint, tested for non-inferiority, was mean change in hemoglobin from baseline to the average during the primary evaluation period (weeks 28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

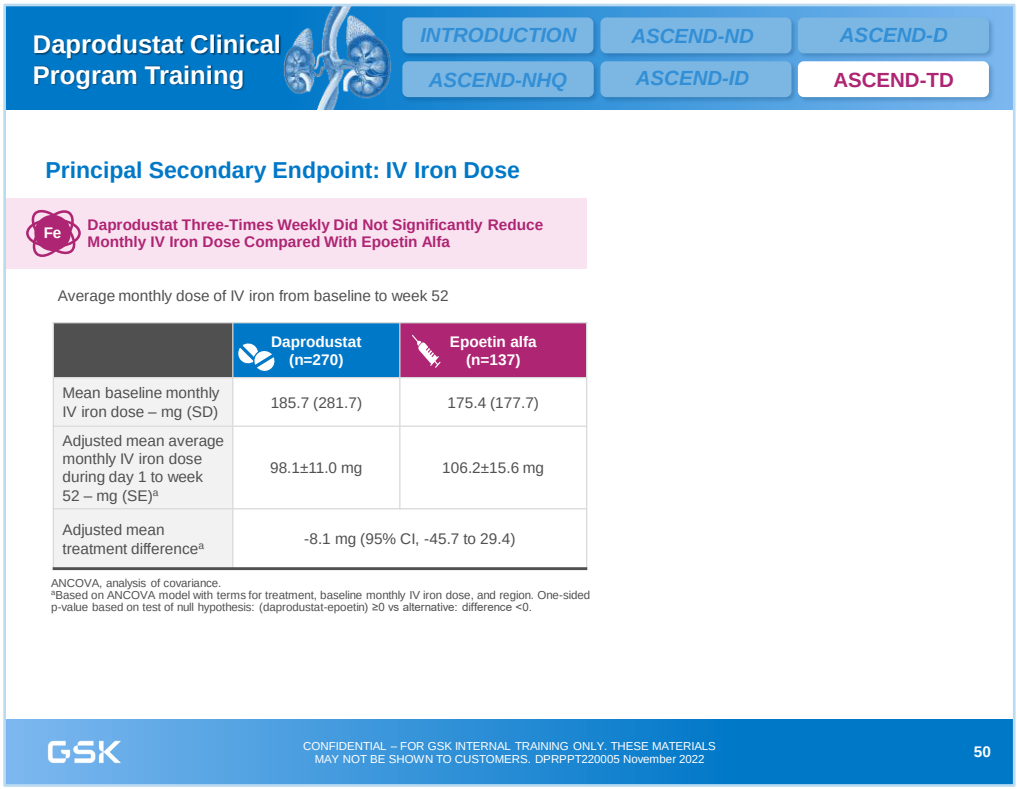


Facilitator Notes

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.*

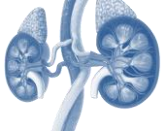


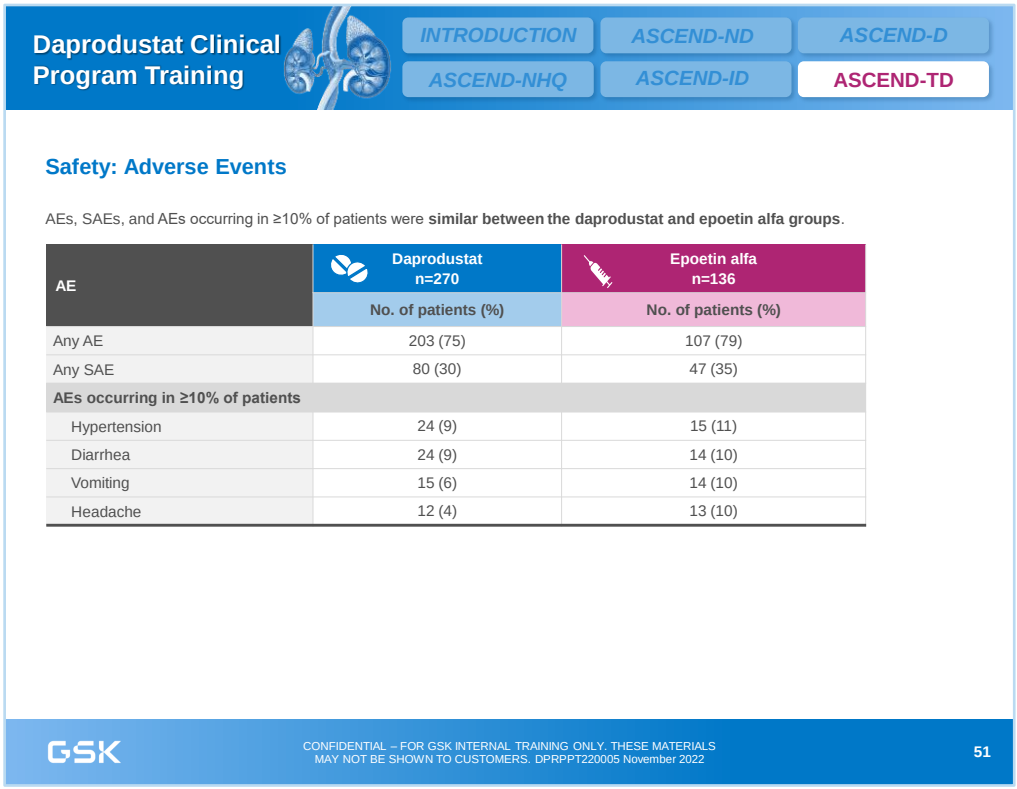


Facilitator Notes

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.*

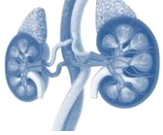




Facilitator Notes

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.*



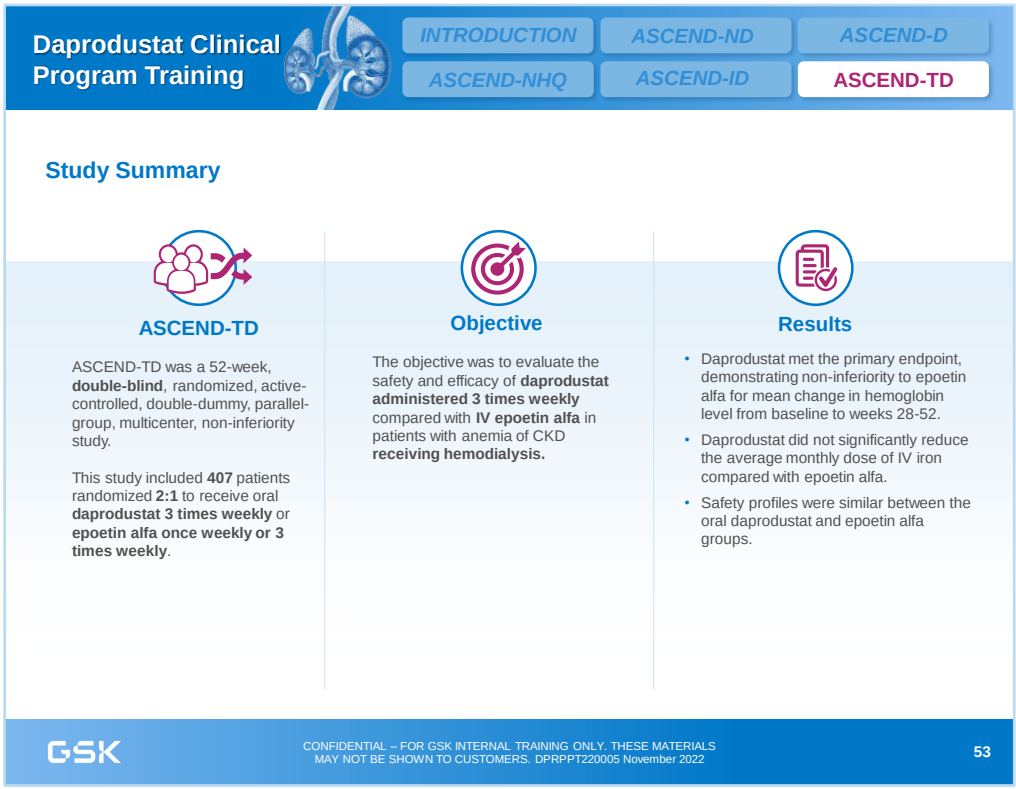
Safety: Adverse Events of Special Interest

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)

Facilitator Notes

Say:

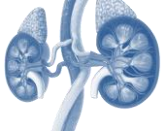
- *Prespecified adverse events of special interest were consistent across the daprodustat and epoetin alfa treatment arms.*



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.*



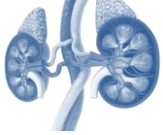
ASCEND Program Summary

	DIALYSIS TRIALS			NON-DIALYSIS TRIALS	
	ASCEND-D	**ASCEND-ID**	**ASCEND-TD**	**ASCEND-ND**	**ASCEND-NHQ**
Comparator	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
Outcomes **Primary Endpoint(s)**	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 24-28.
Principal Secondary Endpoint(s)	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 ≥1 g/dL increase in hemoglobin from baseline **and** change in SF-36 vitality domain score from baseline.
Adverse Events	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.

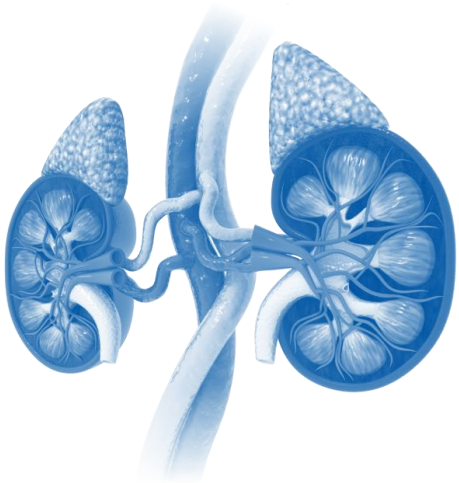
Facilitator Notes

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.