Daprodustat for the Treatment of Anemia of Chronic Kidney Disease

October 26, 2022

GSK

Cardiovascular and Renal Drugs Advisory Committee

Introduction

Janet van Adelsberg, MD

Medicines Development Leader, Daprodustat

Vice President

GSK

Daprodustat: New Oral Treatment for Patients with Anemia of CKD

- Oral option for patients and physicians to individualize care and meet treatment needs
- Member of new drug class: Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI)
  - Increases production of endogenous erythropoietin
- Short half life: 1-4 hours
- Can be administered once daily (QD) or three times weekly (TIW)
  - Effective dose range: 1 to 24 mg (QD), 2 to 48 mg (TIW)
- No need to adjust dose for dialysis or use of phosphate binders and oral iron

Daprodustat Clinical Studies Demonstrated Positive Benefit-Risk Across Populations

Study/ Population	Design	Dosing	Duration	N
ASCEND-NHQ (205270) Not on Dialysis	Randomized (1:1) Double-blind vs placebo Superiority	QD	28 weeks	614
ASCEND-ND (200808) Not on Dialysis	Randomized (1:1) Open-label vs darbepoetin Noninferiority	QD	Event-driven Median = 1.9 yr	3872
ASCEND-ID (201410) Incident dialysis[1]	Randomized (1:1) Open-label vs darbepoetin Noninferiority	QD	52 weeks	312
ASCEND-TD (204837) Hemodialysis	Randomized (2:1) Double-blind vs epoetin Noninferiority	TIW	52 weeks	407
ASCEND-D (200807) Hemodialysis or peritoneal dialysis	Randomized (1:1) Open-label vs epoetin alfa (HD) or darbepoetin (PD) Noninferiority	QD	Event-driven Median = 2.5 yr	2964

1. Dialysis to be initiated within 6 weeks or receiving dialysis treatment for < 90 days

Analysis Definitions

Analysis	Definition	Abbreviation
Primary MACE and other CV events	Events occurring on or after randomization	ITT [1, 2, 3, 4, 5]
On-treatment:	Events occurring on or after treatment start and on or before the earlier of the date of study completion/withdrawal or:	
Pre-specified (CV)	Last dose + 28-day ascertainment period	LDD + 28 days [1, 2, 3, 4, 5]
Pre-specified (TEAE)	Last dose + 1 day ascertainment period	LDD + 1 days [1, 2, 3, 4, 5]
Post-hoc	Last dose + dosing frequency*	LDD + DF [1, 3]
Post-hoc	Last dose + dosing frequency* + 28-day ascertainment period	LDD + DF + 28 days [1, 3]
On- and off-treatment (AE)	Events occurring on or after treatment start	mITT [1, 3]

DF=dosing frequency; LDD=last dose date; CV = cardiovascular; TEAE = treatment emergent AE

*** A participant's dosing frequency at their last dose of randomized treatment was used. Dosing frequency for daily doses = 1 day; TIW doses = 2 days; weekly doses = 7 days; every 2 weeks = 14 days; every 4 weeks = 28 days**

1. GSK Briefing Document; 2. Singh et al, NEJM 2021 (Non-Dialysis); 3. Singh et al, NEJM 2021 (Non-Dialysis Supplemental Material); 4. Singh et al, NEJM 2021 (Dialysis); 5. Singh et al, NEJM 2021 (Dialysis Supplemental Material).

Highlights of the FDA's Briefing Document:

- GSK conducted five adequate and well-controlled trials
  - Key design elements including margins for non-inferiority, endpoints (Hb, MACE), comparators (ESAs) and primary analysis methods (ITT) agreed with FDA
- In ASCEND-ND and ASCEND-D
  - Co-primary objectives met
  - Daprodustat demonstrated non-inferiority relative to ESA controls for CV safety and efficacy based on pre-specified ITT analyses
- Efficacy of daprodustat to raise Hb is not in question
- Agenda will focus on discussion points raised by FDA

Agenda: Important Topics Raised in FDA's Briefing Document

Unmet Need	**Kirsten Johansen, MD** Professor of Medicine, University of Minnesota Nephrology Division Director, Co-Director, Chronic Disease Research Group Hennepin County Medical Center
Clinical Trial Results ▪ Demographics & Disposition, Efficacy including Quality of Life	**Alexander Cobitz, MD, PhD** Clinical Development Lead, Daprodustat Senior Medical Director, GSK
Cardiovascular Safety ▪ Endpoints, Subgroups, Thromboembolism, Heart Failure	**Kaivan Khavandi, MBChB, PhD, MCRP** VP, Clinical Development, GSK
Differential Dosing Frequency & On-Treatment Analysis Bias	**Kevin Carroll, PhD** Chief Statistician KJC Statistics Ltd.
General Safety ▪ Gastric erosions/GI bleeds, Acute Kidney Injury	**Heather Stein, MD** Vice President, Safety Evaluation and Risk Management Global Safety, GSK
Clinical Perspective	**Ajay Singh, MBBS, FRCP** Senior Associate Dean for Postgraduate Medical Education Director, Master in Medical Sciences in Clinical Investigation (MMSCI) Program Harvard Medical School Renal Physician, Brigham and Women's Hospital

External Committee Members Involved With Protocol Development

Executive Steering Committee Members	Ajay Singh	Brigham and Women's Hospital, Boston, MA, USA
	John McMurray	Glasgow University, Glasgow, UK
	Vlado Perkovic	University of New South Wales, Sydney,
	Scott Solomon	Brigham and Women's Hospital, Boston, MA, USA
	Kevin Carroll	KJC Statistics, Cheshire, UK
Steering Committee Members	Ajay Singh	Brigham and Women's Hospital, Boston, MA, USA
	Vivekanand Jha	The George Institute for Global Health, New Delhi, India
	Gregorio T. Obrador	Universidad Panamericana, Mexico City, Mexico
	Christoph Wanner	University Hospital Würzburg, Würzburg, Germany
	Andrzej Wiecek	Medical University of Silesia, Katowice, Poland
	Kirsten L. Johansen	University of Minnesota, Minneapolis, MN, USA
	Sushrut S. Waikar	Boston Medical Center, Boston, MA, USA
	David Wheeler	University College London, London, UK
	Iain Macdougall	King's College Hospital, London, UK
Clinical Events Classification Chair	Renato D. Lopes	Duke Clinical Research Institute, Durham, NC, USA

Additional Experts

Tara Barker, MS
Global Safety
GSK

Allison Blackorby, MS
Statistics
GSK

Tim Hart, PhD
Nonclinical
GSK

Tom Keely, PhD
Health-Related Quality of Life
GSK

Kelly Mahar, PhD
Clinical Pharmacology
GSK

Janet Wittes, PhD
Statistician
Wittes LLC

Vlado Perkovic, MBBS PhD FRACP FASN FAHMS
Cardiorenal Expert
Dean of Medicine and Health, and Scientia Professor
University of New South Wales

Unmet Need for Patients with Anemia of CKD

Kirsten L. Johansen, MD, FASN

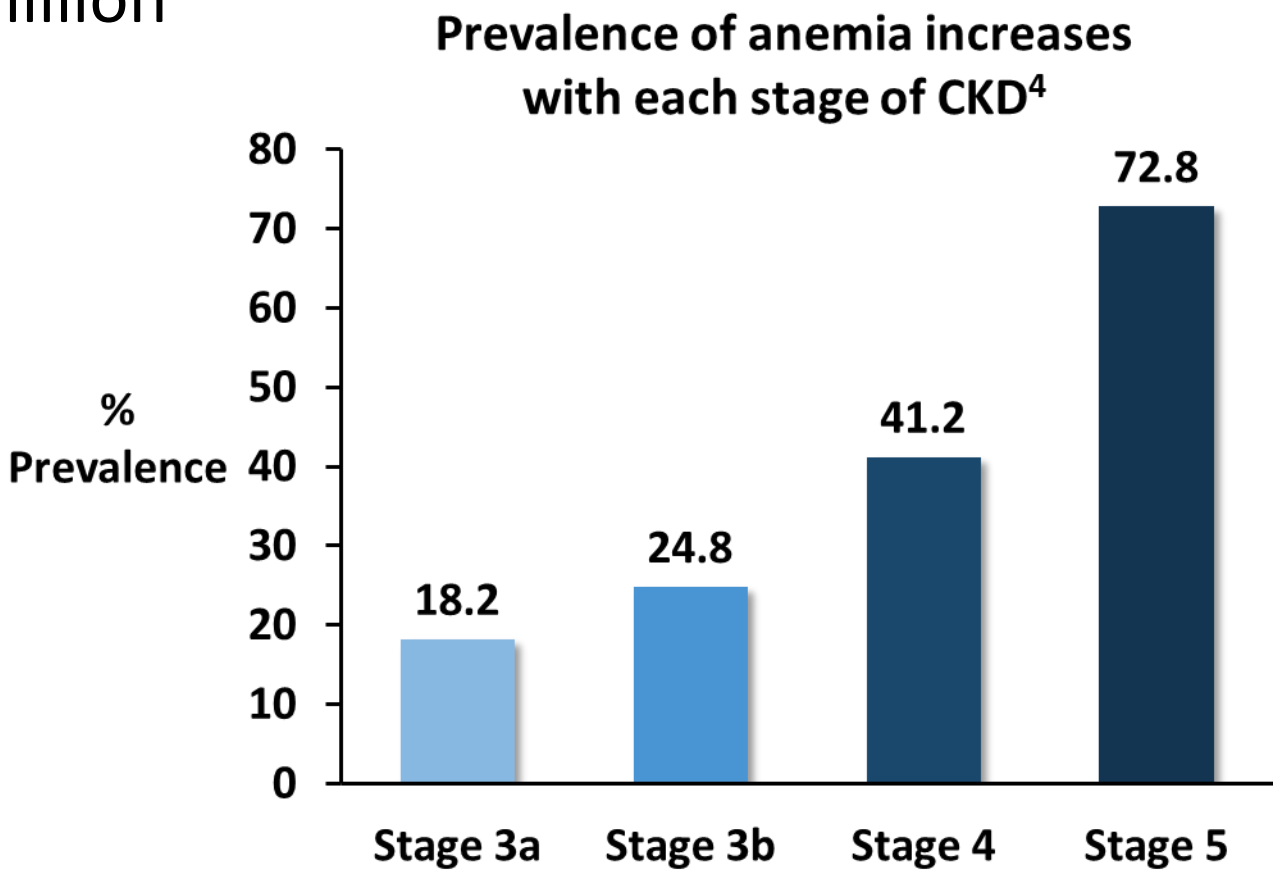
Nephrology Division Director, Hennepin County Medical Center

Co-Director, Chronic Disease Research Group

ASCEND Steering Committee Member

Anemia of CKD is a Significant Public Health Challenge

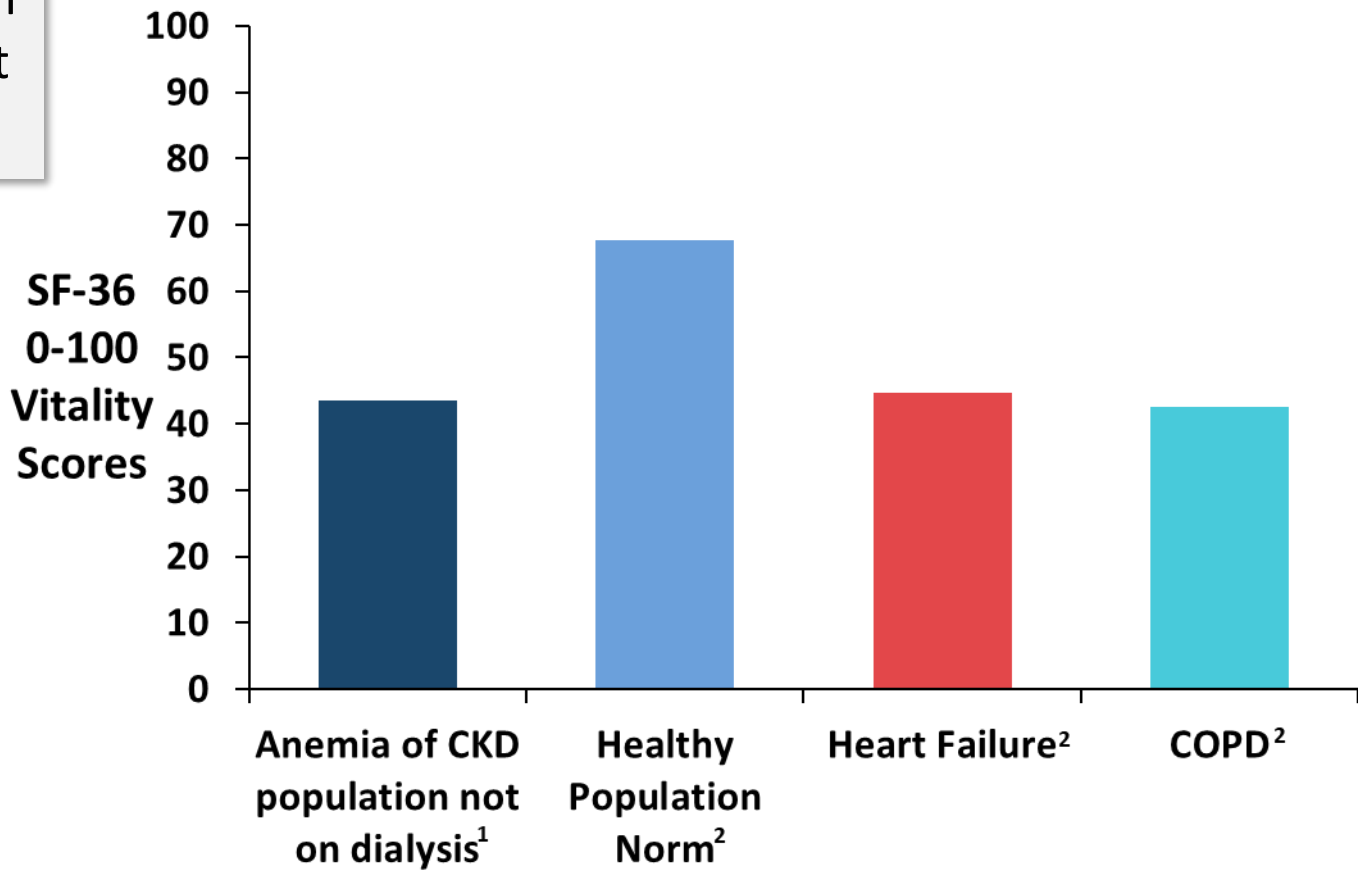
- > 1 in 7 (15%) of US adults or 37 million people, estimated to have CKD[1]
- Anemia of CKD affects 4.8 million patients[2]
- Present in 87% of patients receiving hemodialysis[3]
- Associated with reduced QoL, higher rates of CV comorbidities, hospitalizations, and mortality[4-8]



1. Preventing Chronic Disease (nih.gov) access on June 6, 2022; 2. Stauffer, 2014; 3. USRDS, 2021; 4. Wittbrodt, et al., 2022; 5. Babbit, 2012; 6. Palaka et al. 2020; 7. Thorp et al. 2009; 8. Lamerato et al. 2022;

Comparison of Anemia of CKD Mean SF-36 Vitality Domain Scores with Healthy US Population, Heart Failure, and COPD

- SF-36 vitality domain is robust assessment of fatigue



Anemia of CKD patients have levels of fatigue substantially higher than general population and comparable to HF and COPD populations

1. Finkelstein 2009; 2. GSK Data on File. 2022N518875_00

Significant Barriers to Access Exist

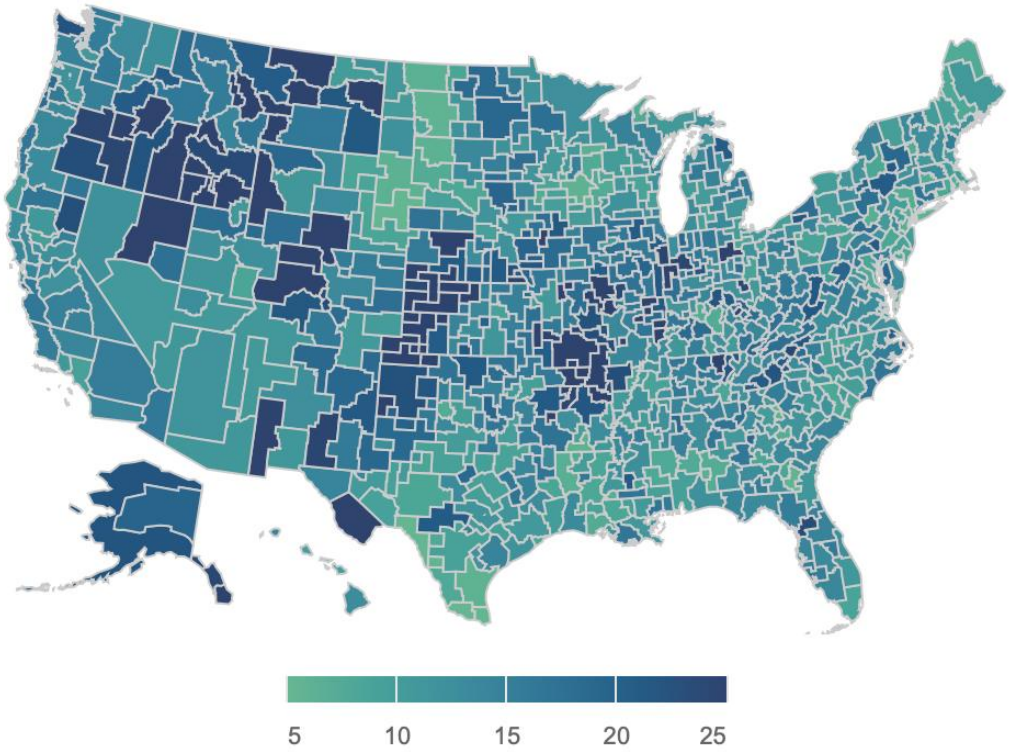
- Currently available therapies are injectable and often require in-clinic administration and cold-chain storage
- Patient preference surveys
  - a significant proportion of patients preferred oral medications over injectable[1]
- Burden falls more heavily on disadvantaged groups, those living in rural areas or who rely on caregivers for transportation[2]

1. Alexandre, et al. Nephro Dialysis Transplantation 2020, 2. Yan, et al. Clin J Am Soc Nephrol 2013

Increasing Use of Home Dialysis in the US

- 13.1% of prevalent dialysis population on home dialysis
- In many regions, particularly rural, 1 in 4 patients on home dialysis
- Patients on home dialysis face barriers related to injectable therapy

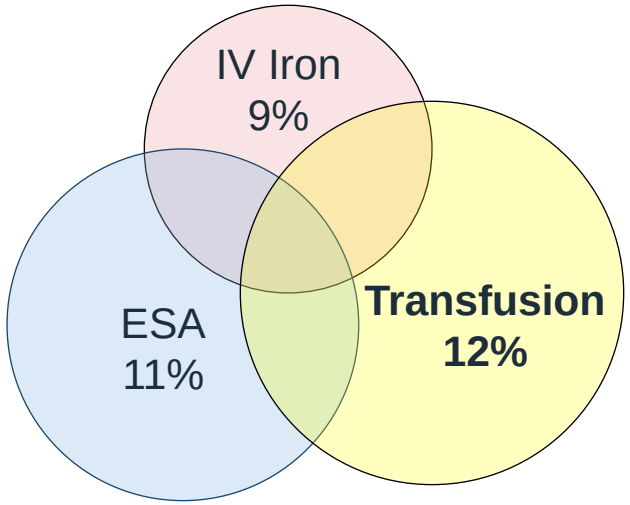
Unadjusted utilization (%) of home dialysis among prevalent ESRD patients undergoing dialysis, 2017-2018



Predominant Treatment in ND Patients is Transfusions

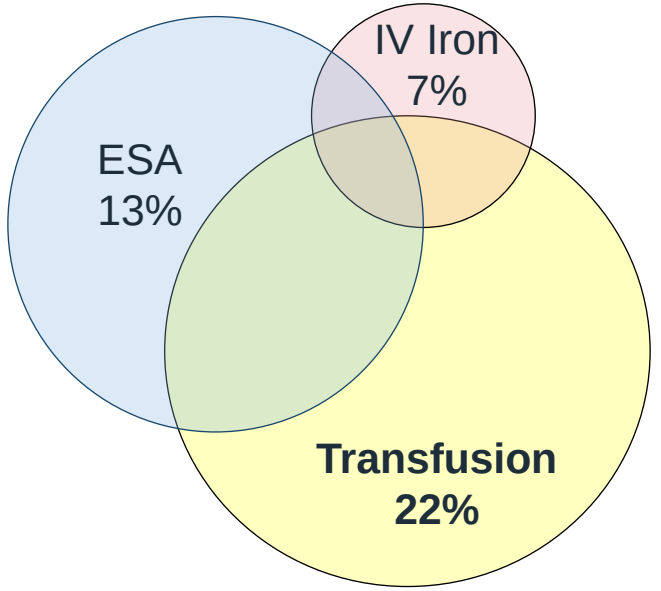
Proportion of stage 3–5 non-dialysis-dependent CKD patients with anemia

Commercially-insured patients Aged 18 – 63



74% of patients were not treated

Medicare-covered patients Aged 66 – 85

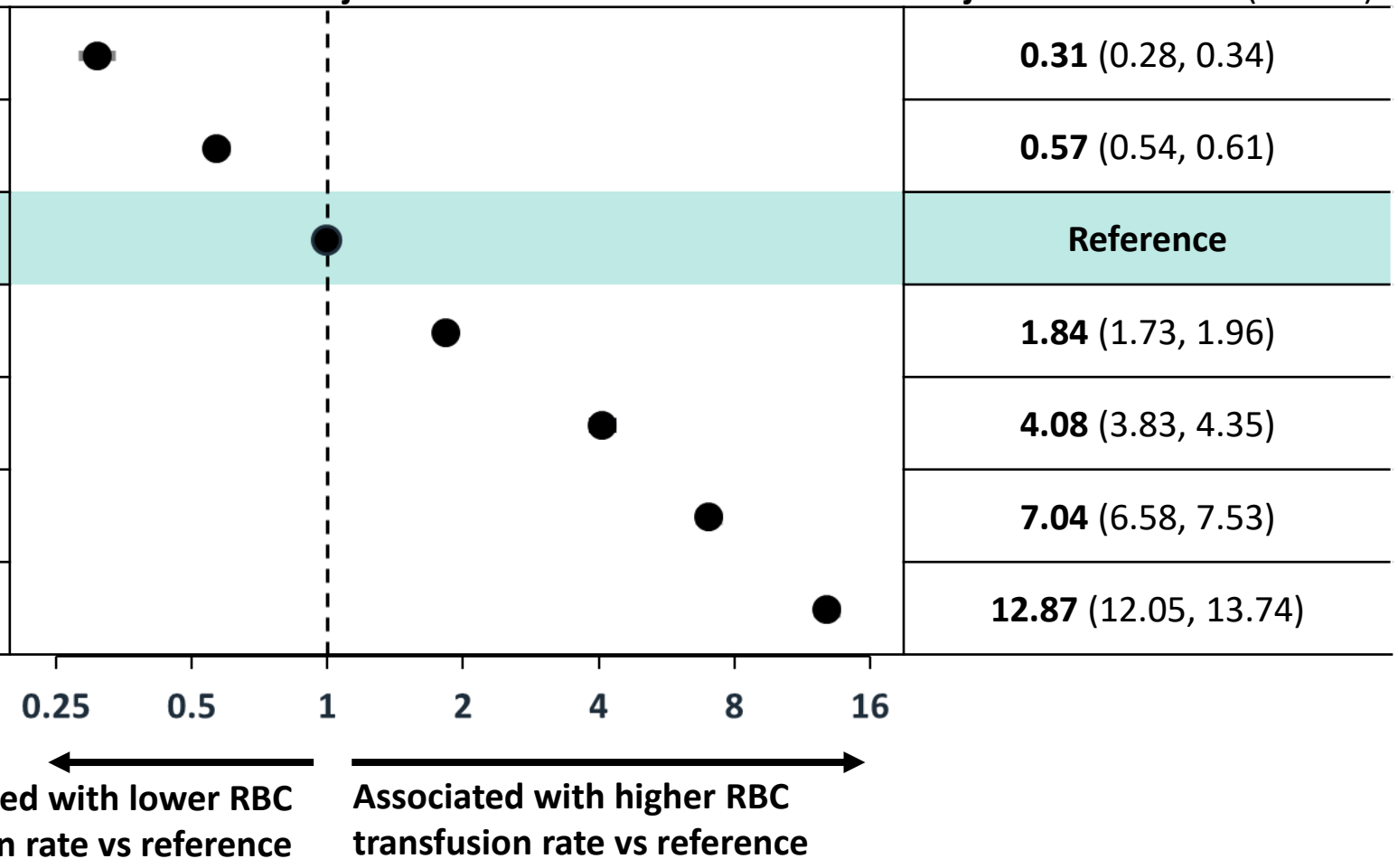


66% of patients were not treated

St. Peter et al, BMC Nephrology, 2018

Incidence of Transfusions Strongly Associated with Hb Level[1]

Baseline Hb (g/dL)	n at risk	Rate per 100PY	Adjusted Rate Ratio (95% CI)
≥ 12.0	13,757	4.2	**0.31** (0.28, 0.34)
11.0 – 11.99	27,702	6.3	**0.57** (0.54, 0.61)
10.0 – 10.99	12,979	12.0	**Reference**
9.0 – 9.99	5,697	24.5	**1.84** (1.73, 1.96)
8.0 – 8.99	2,588	61.5	**4.08** (3.83, 4.35)
7.0 – 7.99	1,101	112.9	**7.04** (6.58, 7.53)
< 7.0	730	191.7	**12.87** (12.05, 13.74)



1. Adjusted for age, sex, CKD stage, Charlson Comorbidity Index, baseline comorbidities, baseline HCRU, prior RBC transfusion use, prior ESA or oral/IV iron use 1 Data on File. 2022N518136_00

Transfusion Associated With Short and Long-term Risks

Short-term risks[1]

- Infections
- Volume overload
- Hospitalization for heart failure
  (RR=1.7, 95% CI: 0.3, 9.2)
- Hyperkalemia
  (RR=12.0, 95% CI: 1.3 to 109)

Sensitization[2]

- 26-38% of patients sensitized after a single transfusion vs 2-6% of patients without transfusion

Longer-term risks[3,4]

- Less access to living donors
- Risk of rejection
  - Increased immunosuppression
  - Risk of infection and malignancies

1. Gill, 2015; 2. Lefell, 2014; 3. Schinstock, 2019; 4. Clayton, 2017

Significant Unmet Need in Treatment of Anemia of CKD

- Underutilized injectable therapies in large subset of patients
- Undertreated patients
  - suffer lower QoL
  - at higher risk of receiving transfusions
- Logistical challenges impact vulnerable patients more

There remains a significant need for novel, accessible treatment options for this patient population

Clinical Trial Results

Alexander R. Cobitz, MD, PhD

Clinical Development Lead, Daprodustat

Senior Medical Director

GSK

Clinical Endpoints Across ASCEND Studies

	ASCEND-NHQ N = 614	ASCEND-ND N = 3,872	ASCEND-D N = 2,964	ASCEND-TD N = 407	ASCEND-ID N = 312
Primary	**Efficacy:** Mean change in Hgb from baseline to the average during the primary evaluation period (non-inferiority*)				
		Safety: Time to first Adjudicated MACE (non-inferiority)			
Principal Secondary	**Efficacy:** ▪ Mean change in SF-36 Vitality ▪ Hgb increase of ≥ 1 g/dL	**Safety:** ▪ MACE (superiority) ▪ MACE + thromboembolic events ▪ MACE + hospitalization for heart failure			
		Safety: ▪ Time to CKD progression			
Secondary / Exploratory		**Efficacy:** ▪ % within Hgb target range ▪ % with first occurrence of RBC or whole blood transfusion on-treatment			

* Superiority for NHQ

ASCEND-NHQ

Double-blind, placebo-controlled study in patients not on dialysis

Daprodustat Superior to Placebo for Hgb Change from Baseline With Fewer Transfusions in Daprodustat vs. Placebo

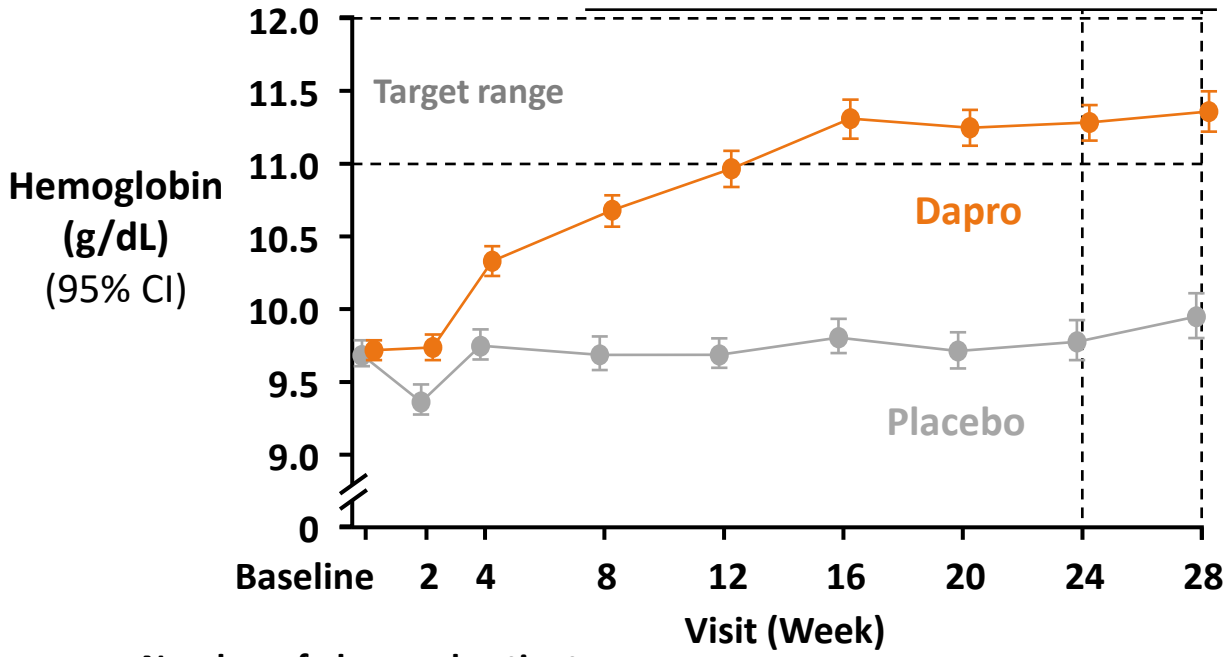
ASCEND-NHQ

Adjusted mean change (Daprodustat-placebo)

1.40 (95% CI: 1.23, 1.56)

One-sided p-value

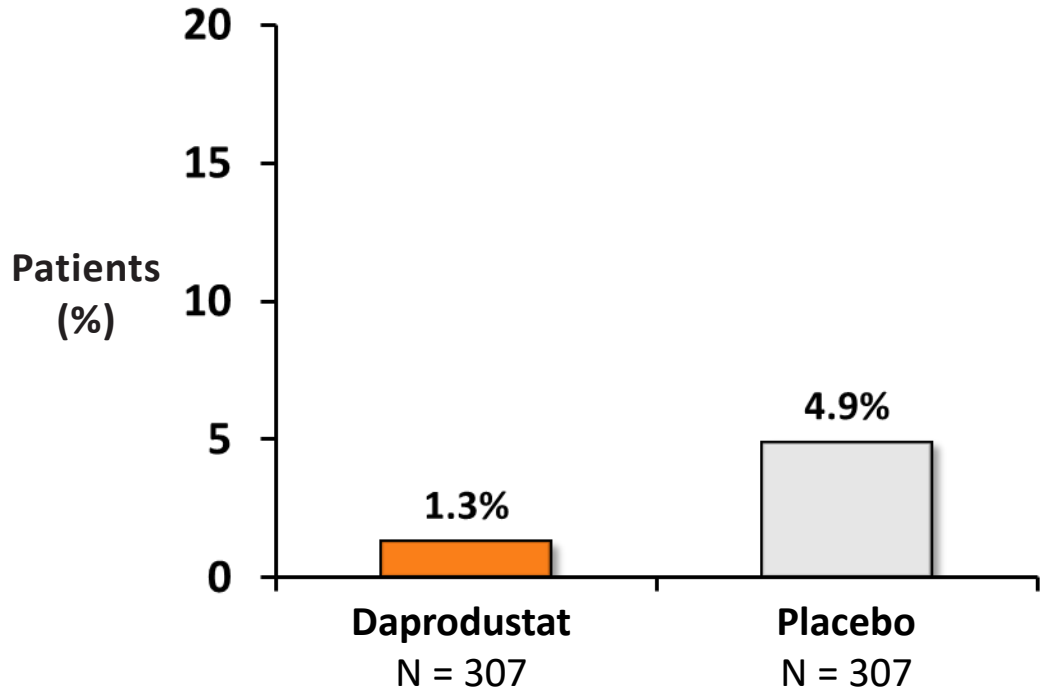
< 0.0001



Number of observed patients

Dapro	307	295	291	283	274	280	265	264	266
Placebo	307	292	290	270	253	269	231	250	255

Patients who received blood transfusion while on-treatment



	Daprodustat	Placebo
Hgb during EP, mean	11.3 g/dL	9.9 g/dL

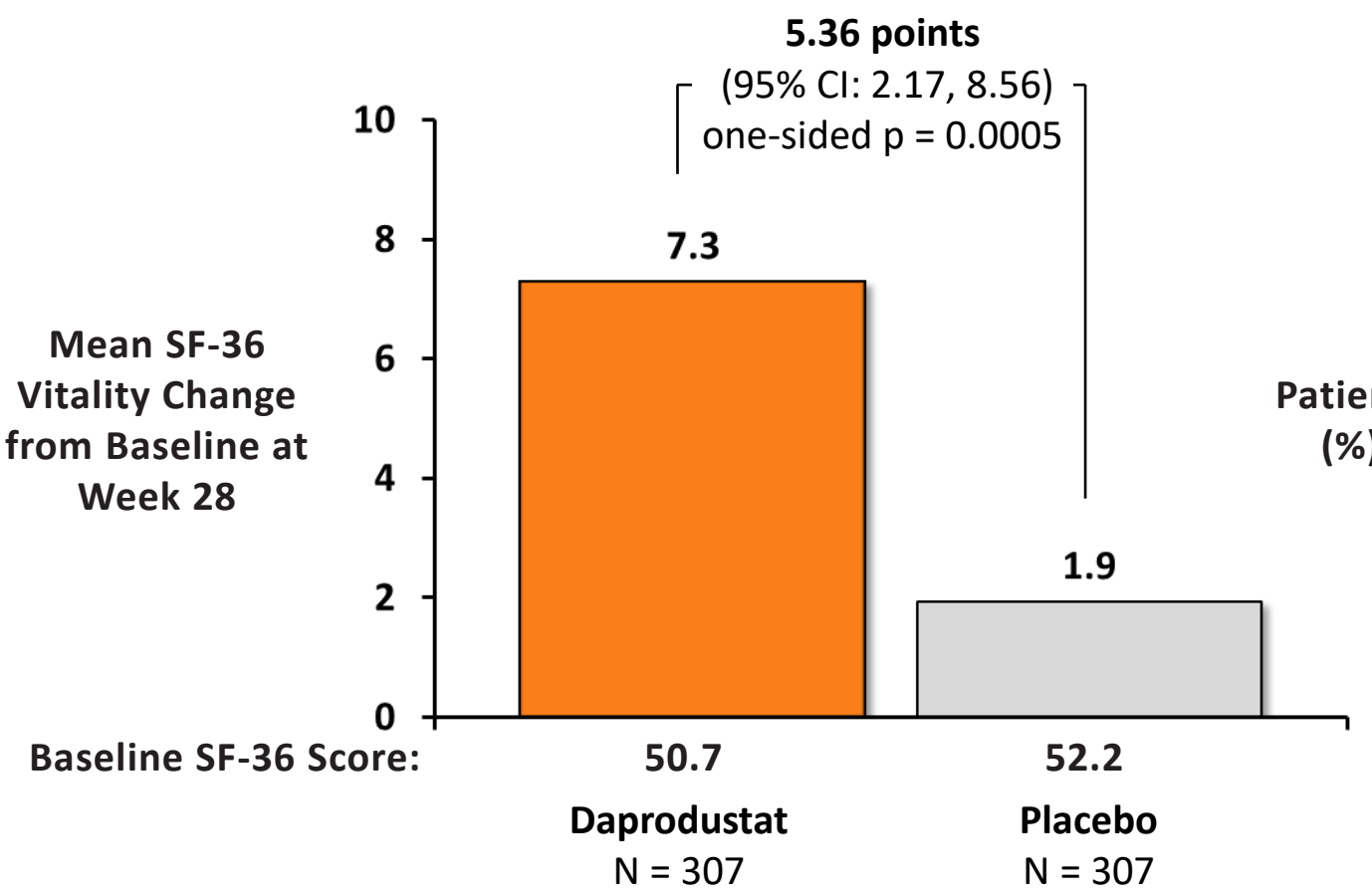
Note: ITT Hgb analysis including observed and imputed data. On-treatment summary of transfusions. EP = Evaluation Period (Weeks 24 – 28)

Daprodustat Superior to Placebo in Improving SF-36 Vitality Score

ASCEND-NHQ

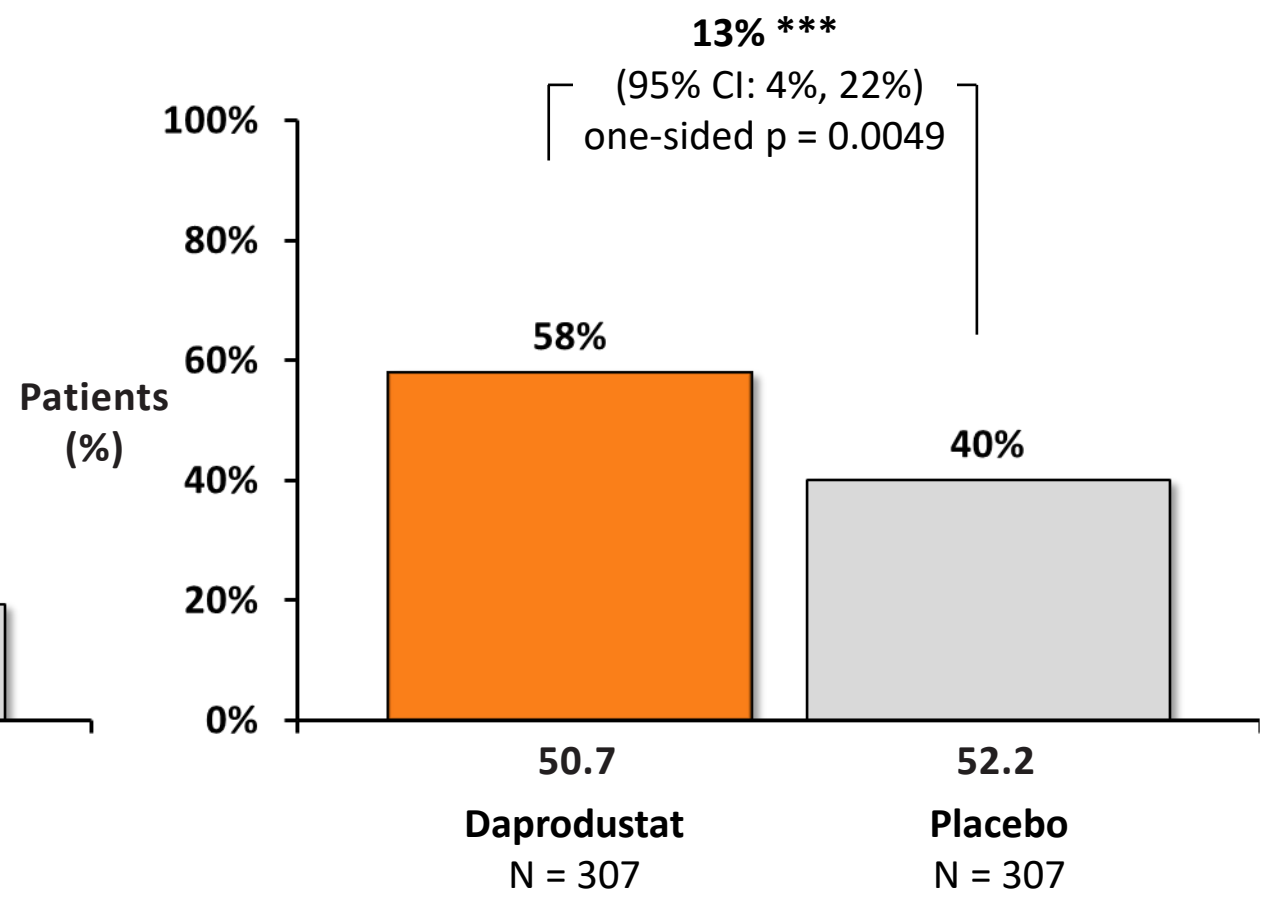
SF-36 Vitality Domain Score Change From Baseline

(Pre-specified Principal Secondary Analysis)*



% of Patients with SF-36 Vitality Change ≥ 6 points

(Pre-specified Additional Secondary Analysis)**



Notes: Scoring 0 to 100.
Data after treatment discontinuation/rescue were imputed in these analyses. 35% of patients had imputed values.

* Endpoint was adjusted for multiplicity

** Endpoint was not adjusted for multiplicity

***Model-adjusted value using imputed data

Active-Controlled Studies

ASCEND-ND, ASCEND-ID, ASCEND-TD, ASCEND-D

Key Design Elements of Active-Controlled Phase 3 Studies

- Major exclusions included
  - Class IV heart failure, recent MI, acute coronary syndrome or stroke, uncontrolled hypertension
- Patients remained in study even if discontinued randomized treatment
- ND patients remained in study if dialysis initiated or changed

Exposure, Demographics and Baseline Characteristics

- > 6000 patients treated with daprodustat resulting in ~6700 PY exposure
  - ~ 1500 patients treated >2 years
- Demographics and baseline characteristics similar between treatment groups
  - Representative of US population with CKD
- Renal characteristics generally similar between treatment groups
- Baseline CV characteristics well-balanced
  - Patients frequently had history of hypertension, diabetes and CV disease

Baseline Characteristics of US Patients

ITT		ASCEND-ND		ASCEND-D	
		Dapro N = 492	Darbe N = 489	Dapro N = 425	ESA N = 421
Mean age		67.5	67.5	58.2	58.1
Gender - Female		45%	45%	44%	42%
Black or African American in US region		33%	33%	40%	38%
Diabetes		67%	70%	68%	67%
Stroke		8%	8%	8%	10%
MI		8%	9%	10%	11%
Cancer		9%	6%	6%	4%
Heart failure		21%	17%	25%	25%
Current hypertension		97%	97%	96%	97%
Hospitalization within 6m prior to screening		10%	6%	10%	11%
Baseline CKD Stage	Stage 2/3	22%	26%	-	-
	Stage 4	52%	53%	-	-
	Stage 5	27%	21%	-	-

Post-hoc

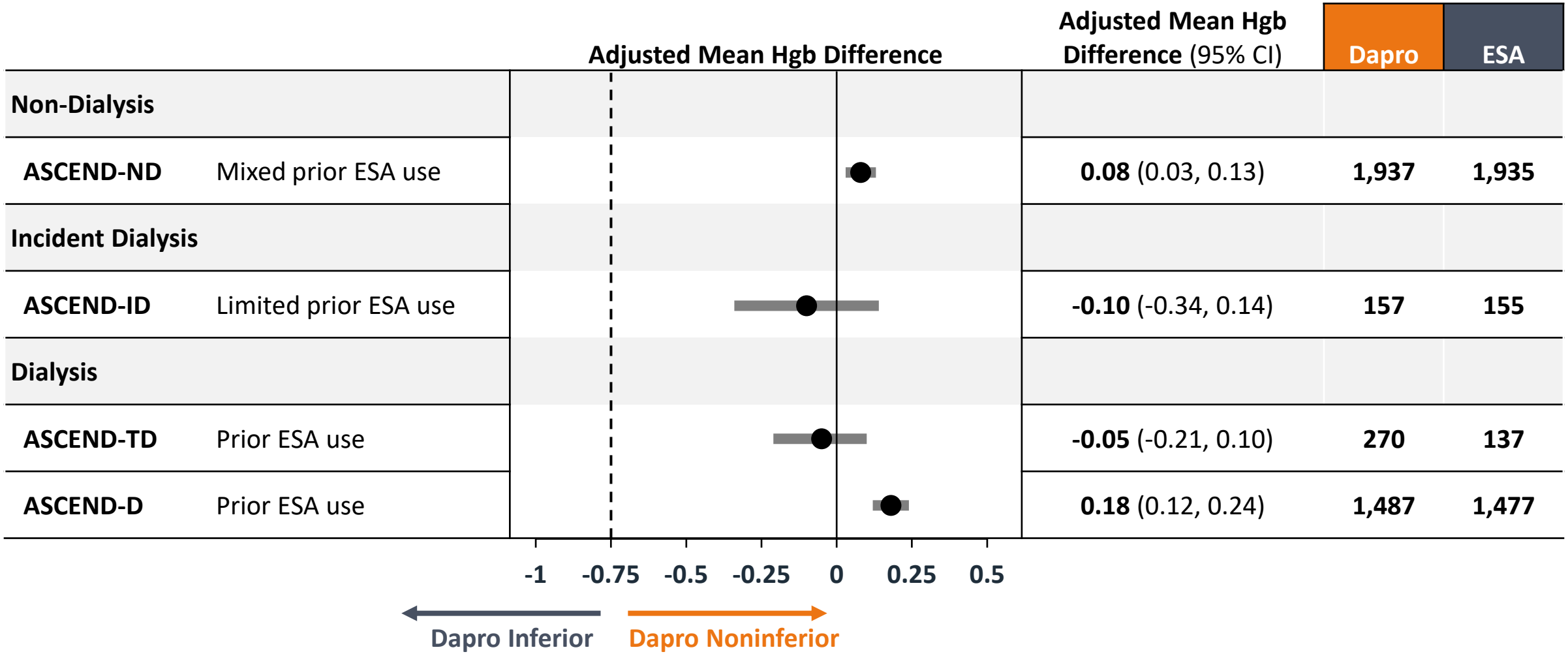
Disposition: High Study Completion Across Active-Controlled Studies

ITT	ASCEND-ND N = 3,872		ASCEND-ID N = 312		ASCEND-TD N = 407		ASCEND-D N = 2,964	
	Dapro	Darbe	Dapro	Darbe	Dapro	ESA	Dapro	ESA
Randomized, n	1,937	1,935	157	155	270	137	1,487	1,477
Completed study	97%	97%	99%	97%	> 99%	99%	92%	92%
Vital status known	> 99%	> 99%	100%	> 99%	100%	100%	98%	98%
Discontinued treatment*	38%	38%	29%	25%	29%	28%	53%	53%
Adverse event	13%	11%	12%	6%	10%	8%	16%	16%
Stopping criteria met	8%	8%	5%	6%	9%	10%	16%	15%
Other**	17%	18%	11%	14%	10%	10%	21%	22%
Began dialysis	35%	34%	-	-	-	-	-	-

* Includes patients who died while taking treatment. If these patients are excluded: ND: 29%, 29%; ID: 22%, 21%; TD: 26%, 26%; D: 45%, 45%.
**Other also includes: lost to follow-up, sponsor terminated study treatment, investigative site closed, missing.

Daprodustat Non-Inferior to ESA for Primary Hgb Endpoints

Active-Controlled Studies

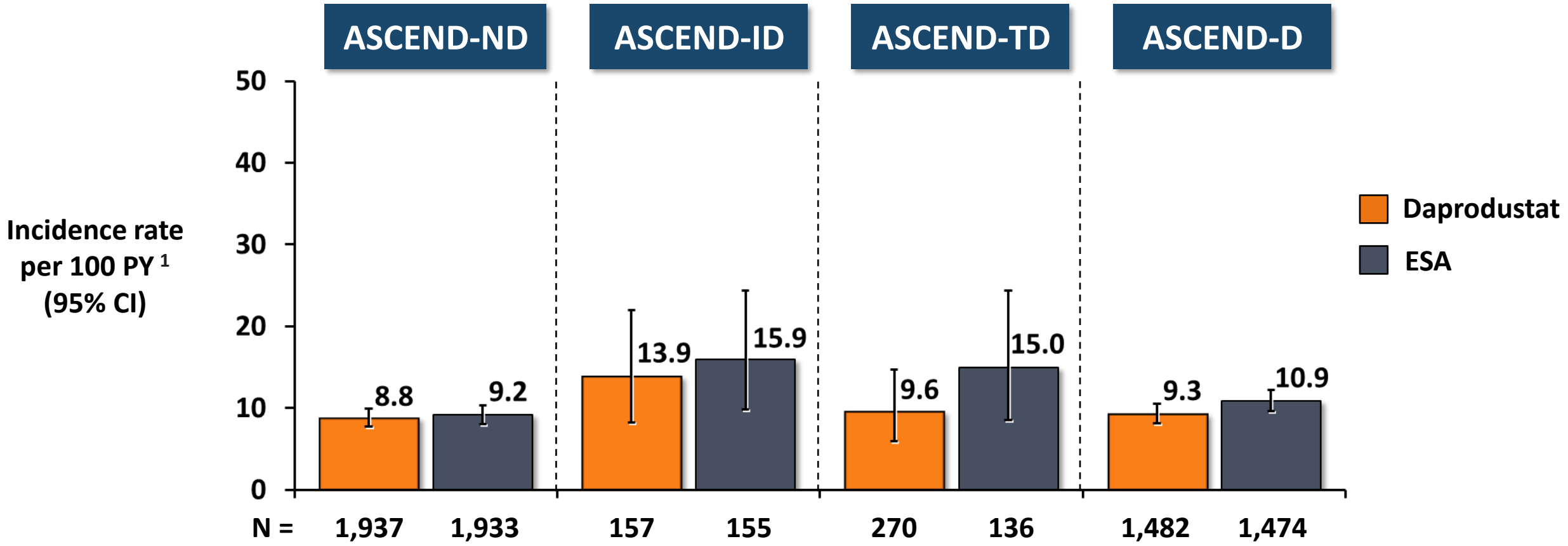


Note: ITT Hgb analyses including observed and imputed data.

ASCEND-ND vs darbepoetin alfa; ASCEND-ID vs darbepoetin alfa; ASCEND-D vs recombinant human erythropoietin; ASCEND-TD vs recombinant human erythropoietin

Similar Incidence of First Transfusion Across Treatment Groups

Active-Controlled Studies



1. First occurrence of RBC or whole blood transfusion during on-treatment period

ASCEND-TD vs darbepoetin alfa; ASCEND-ID vs darbepoetin alfa; ASCEND-D vs recombinant human erythropoietin, ASCEND-ND vs darbepoetin alfa

Efficacy Summary

- Daprodustat met primary Hgb endpoint in all 5 phase 3 trials
- Daprodustat superior to placebo and non-inferior to ESA
  - Achieved and maintained target Hgb levels
- Daprodustat superior to placebo in improving vitality on SF-36
- Fewer daprodustat-treated patients had transfusions than placebo

Cardiovascular Safety

Kaivan Khavandi, MBChB, PhD, MRCP

Disease Area Head, Cardiovascular

Vice President, Clinical Development

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Major Adverse Cardiovascular Events (MACE): Co-Primary Safety Endpoint in 2 CV Outcomes Trials: ASCEND-ND, ASCEND-D

- Composite measure of
  - All-cause mortality (ACM)
    - Precedented in trials of anemia of CKD: agreed with FDA
  - Non-fatal myocardial infarction (MI)
  - Non-fatal stroke
- Clinical Events Classification group
  - Duke Clinical Research Institute – external and independent
  - Blinded to treatment allocation
  - Adjudicated all events that might have constituted MACE

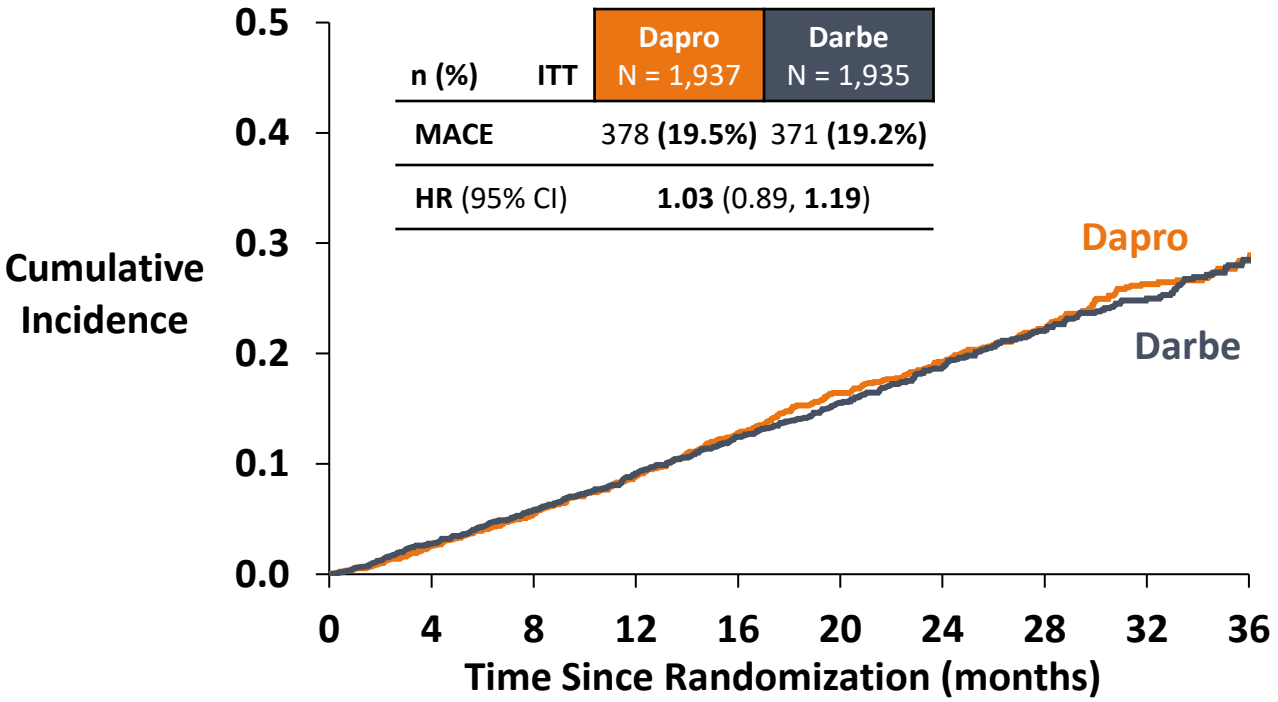
MACE Statistical Assumptions in CVOT Studies ASCEND-ND, ASCEND-D

- Non-inferiority design using ITT approach to preserve the balance afforded by randomization
- Cox Proportional Hazards regression model adjusted for treatment and randomization stratification factors
- Non-inferiority established if upper limit of two-sided 95% CI for the hazard ratio < 1.25
  - Prospectively defined
  - Agreed with FDA

MACE: Daprodustat Non-Inferior to ESA on Co-Primary Endpoint in ASCEND-ND and ASCEND-D

ASCEND-ND

n (%) ITT	Dapro N = 1,937	Darbe N = 1,935
MACE	378 **(19.5%)**	371 **(19.2%)**
HR (95% CI)	**1.03** (0.89, **1.19**)	

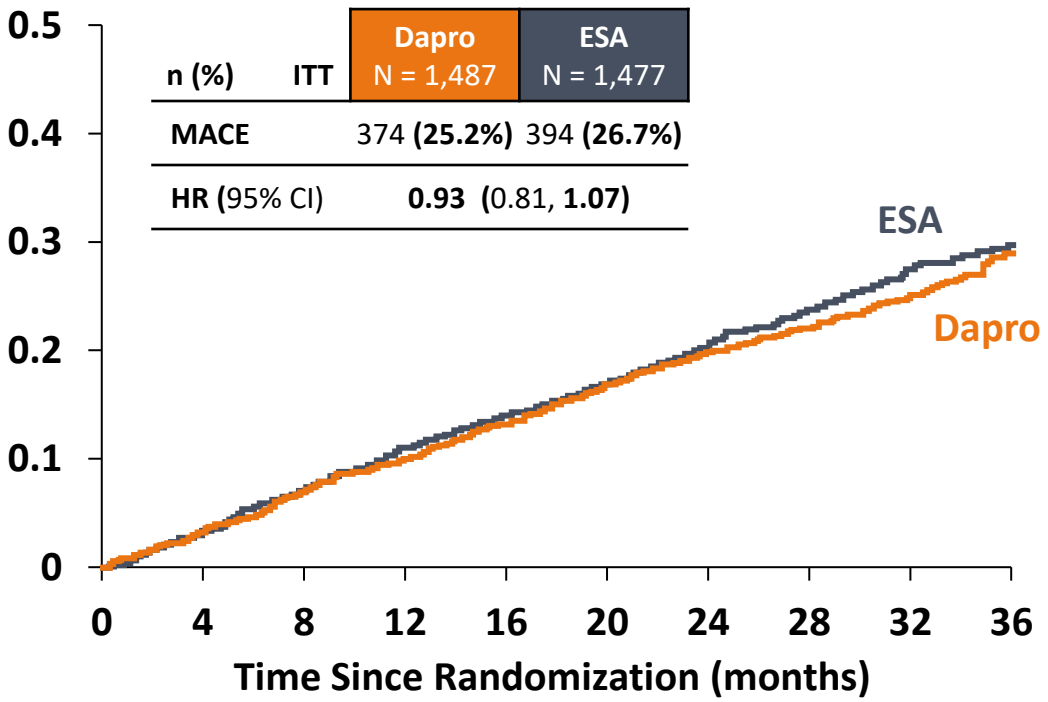


Patients at risk

Dapro	1937	1834	1601	1414	1207	1024	840	647	468	288
ESA	1935	1825	1582	1412	1221	1038	843	660	474	291

ASCEND-D

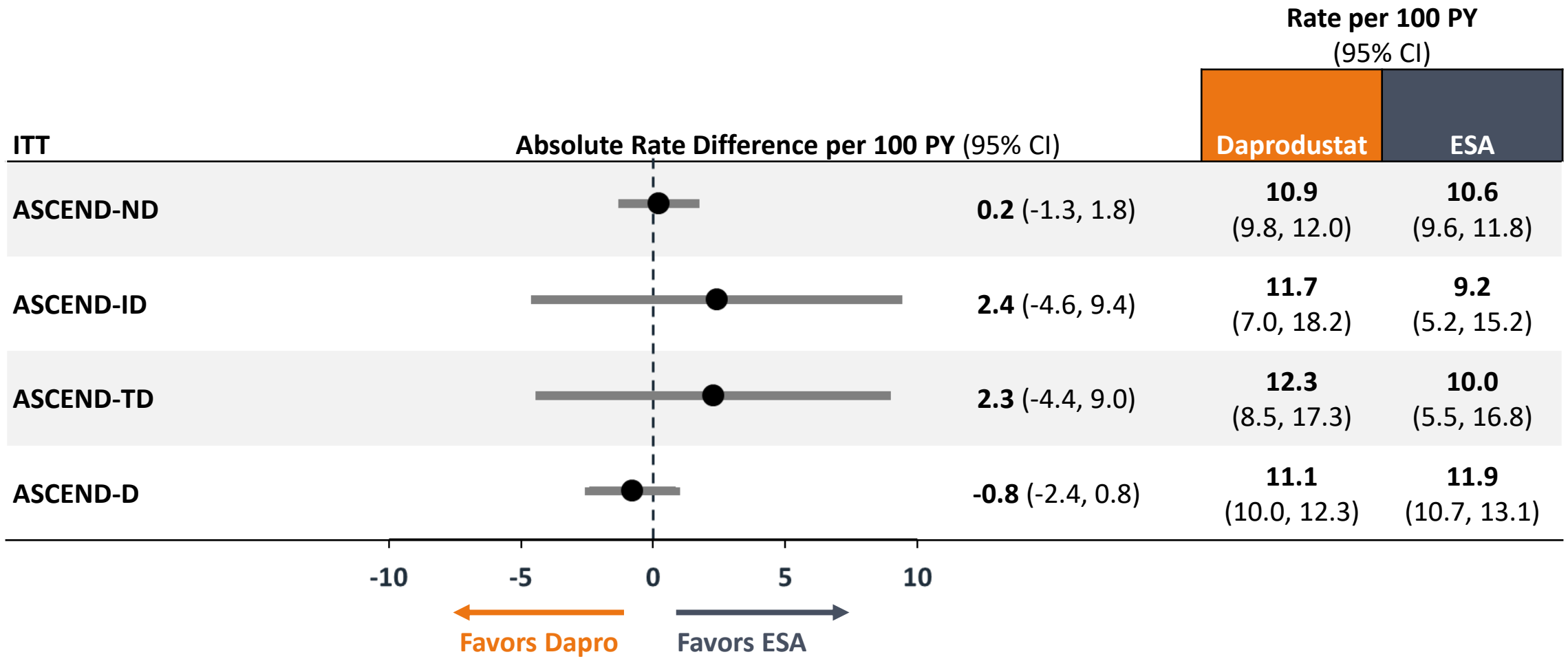
n (%) ITT	Dapro N = 1,487	ESA N = 1,477
MACE	374 **(25.2%)**	394 **(26.7%)**
HR (95% CI)	**0.93** (0.81, **1.07**)	



Dapro	1487	1425	1352	1297	1240	1181	1129	861	559	250
ESA	1477	1427	1348	1271	1217	1170	1108	836	525	245

Non-inferiority established for MACE upper limit of 2-sided 95% CI for HR lower than pre-specified 1.25 margin

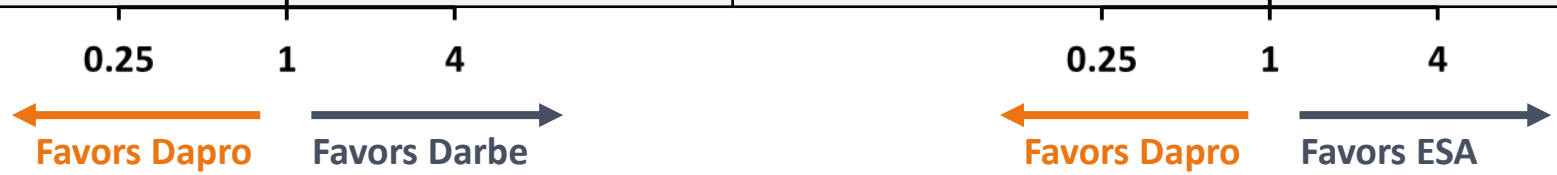
Consistent MACE Findings in Daprodustat CVOTs and All Other ASCEND Studies



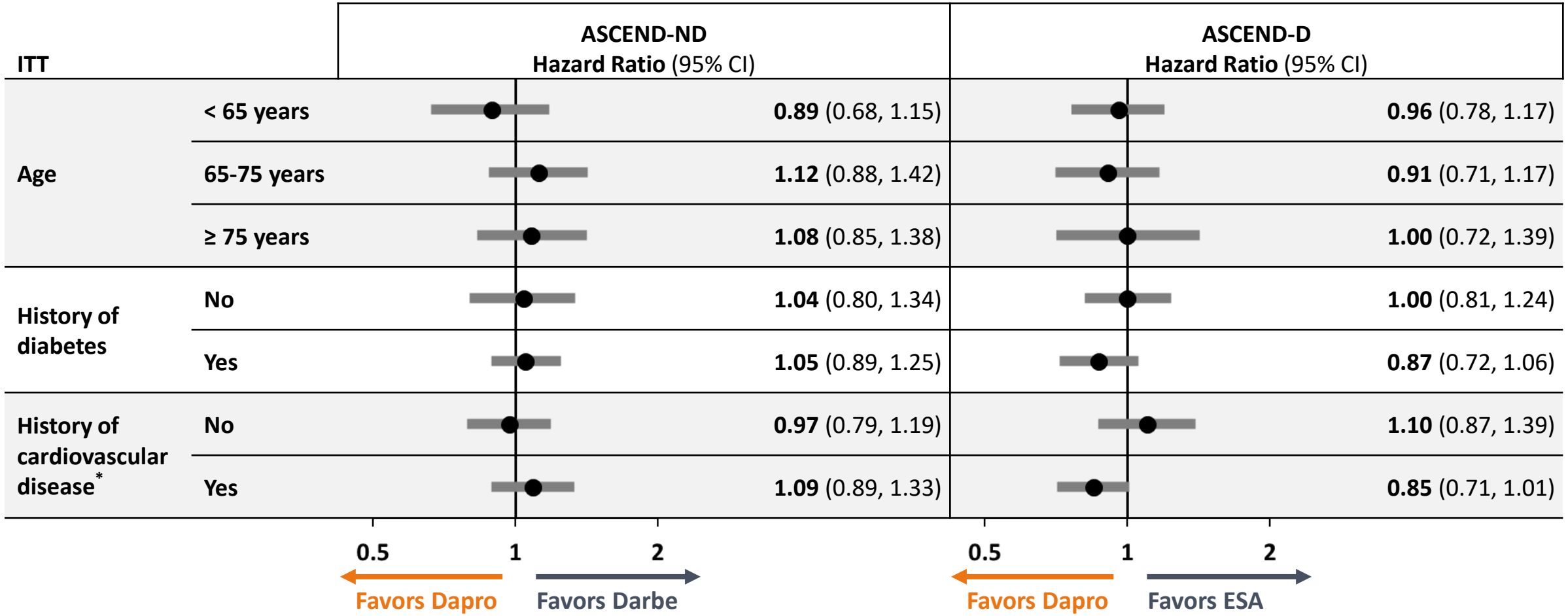
ASCEND-NHQ (28 weeks), First MACE rates: **4.9% Daprodustat; 6.2% placebo**

MACE by Regional Subgroups in ASCEND-ND and ASCEND-D

ITT	ASCEND-ND Dapro n/N	ASCEND-ND Darbe n/N	ASCEND-ND Hazard Ratio (95% CI)	ASCEND-D Dapro n/N	ASCEND-D ESA n/N	ASCEND-D Hazard Ratio (95% CI)
Asia Pacific	56/494	78/494	**0.70** (0.49, 0.98)	20/142	33/143	**0.59** (0.34, 1.03)
Eastern Europe/ South Africa	67/344	59/343	**1.18** (0.83, 1.68)	92/419	82/416	**1.14** (0.84, 1.53)
Western Europe/ Canada/ ANZ/ Israel	57/312	62/314	**0.88** (0.61, 1.25)	68/288	92/284	**0.70** (0.51, 0.96)
Latin America	78/295	67/295	**1.22** (0.88, 1.69)	57/213	48/213	**1.19** (0.81, 1.74)
USA	120/492	105/489	**1.19** (0.91, 1.54)	137/425	139/421	**0.96** (0.75, 1.21)



No Clinical Features Associated with Treatment Group Difference for MACE Compared with Primary Analysis



*CVD history was defined as having a yes response to any of the following medical history conditions: angina pectoris, myocardial infarction, stroke, coronary artery disease, transient ischemic attack, heart failure, atrial fibrillation, cardiac arrest, and/or valvular heart disease.

All-Cause Mortality: Similar Between Treatment Groups in Non-Dialysis and Dialysis Patients

Adjudicated Cause of death, N (%) ITT	ASCEND-ND		ASCEND-D	
	Dapro N = 1,937	Darbe N = 1,935	Dapro N = 1,487	ESA N = 1,477
All cause mortality	301 **(15.5%)**	298 **(15.4%)**	294 **(19.8%)**	300 **(20.3%)**
Cardiovascular	89 **(4.6%)**	70 **(3.6%)**	96 **(6.5%)**	91 **(6.2%)**
Non-cardiovascular	149 **(7.7%)**	148 **(7.6%)**	132 **(8.9%)**	155 **(10.5%)**
Undetermined	63 **(3.3%)**	80 **(4.1%)**	66 **(4.4%)**	54 **(3.7%)**

CV Mortality, rather than ACM:

- Analysis includes deaths with a CV primary cause of death + undetermined deaths with presumed sudden/CV primary cause of death [ASCEND-ND: 20 (dapro), 22 (darbe); ASCEND-D: 21 (dapro), 30 (ESA)]
- Excludes ~2/3 deaths
- Assumes deaths are non-informative, i.e., entirely independent of disease status, or randomized treatment

Fatal/Non-Fatal MI: Generally Similar Incidence Between Treatment Groups

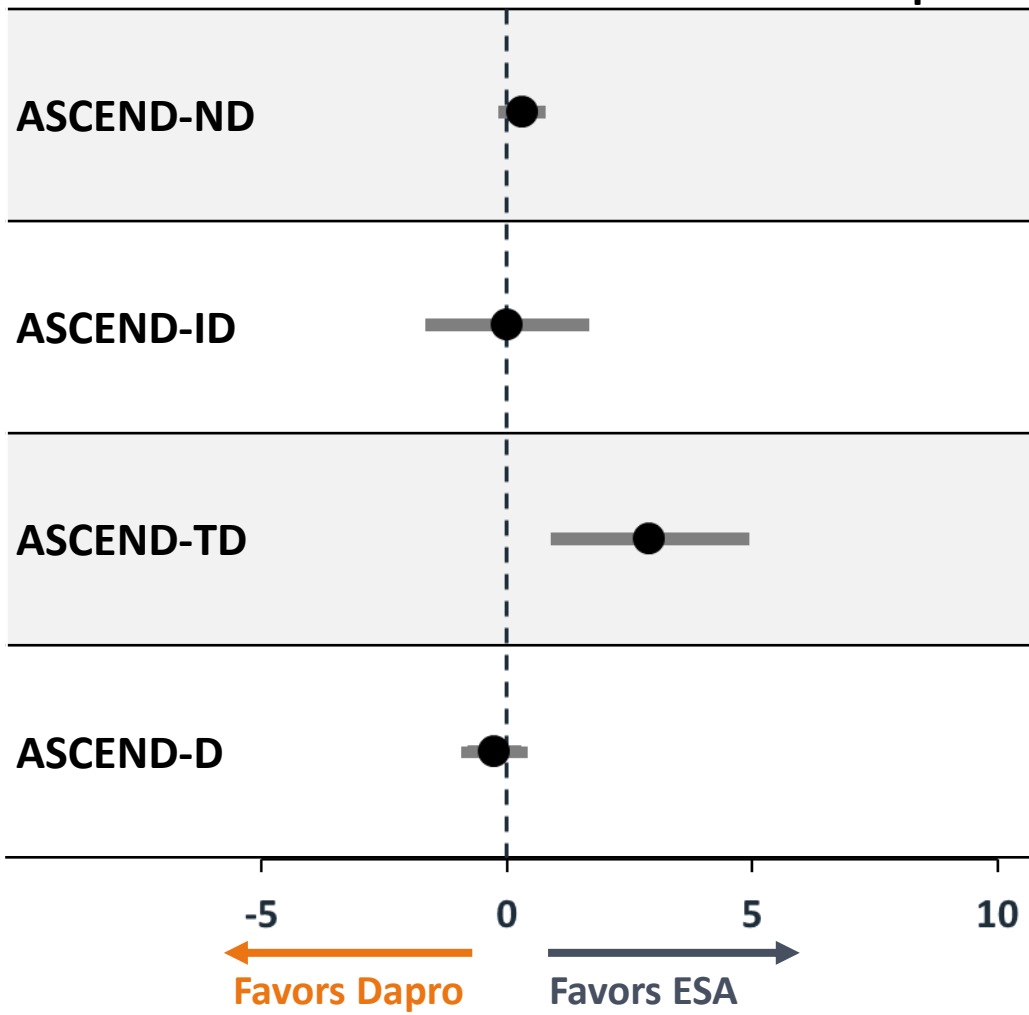
ITT	ASCEND-ND		ASCEND-D	
	Daprodustat N = 1,937	Darbepoetin N = 1,935	Daprodustat N = 1,487	ESA N = 1,477
First occurrence of adjudicated MI (fatal or non-fatal) n (%)	103 **(5.3%)**	97 **(5.0%)**	114 **(7.7%)**	137 **(9.3%)**
Incidence rate per 100 PY (95% CI)	**2.94** (2.40, 3.56)	**2.76** (2.24, 3.36)	**3.34** (2.76, 4.01)	**4.08** (3.43, 4.83)
Absolute rate difference per 100 PY (95% CI)	**0.18** (-0.61, 0.97)		**-0.74** (-1.66, 0.18)	
Hazard ratio (95% CI)	**1.06** (0.80, 1.40)		**0.81** (0.63, 1.04)	

Fatal/Non-Fatal Stroke: Incidence Rate Across Studies

ITT	ASCEND-ND		ASCEND-D	
	Daprodustat N = 1,937	Darbepoetin N = 1,935	Daprodustat N = 1,487	ESA N = 1,477
First occurrence of adjudicated stroke (fatal or non-fatal) n (%)	45 **(2.3%)**	34 **(1.8%)**	43 **(2.9%)**	51 **(3.5%)**
Incidence rate per 100 PY (95% CI)	**1.26** (0.92, 1.69)	**0.95** (0.66, 1.33)	**1.23** (0.89, 1.66)	**1.48** (1.10, 1.94)
Absolute rate difference per 100 PY (95% CI)	**0.31** (-0.18, 0.80)		**-0.25** (-0.79, 0.30)	
Hazard ratio (95% CI)	**1.33** (0.85, 2.07)		**0.84** (0.56, 1.25)	

Stroke Findings in ASCEND Program

ITT	Absolute Rate Difference per 100 PY (95% CI)		Dapro	ESA
ASCEND-ND	0.3 (-0.2, 0.8)	Events, n (%)	45 (2%)	32 (2%)
		Rate per 100 PY	**1.3**	**1.0**
		95% CI	0.9, 1.7	0.7, 1.3
ASCEND-ID	0 (-1.7, 1.7)	Events, n (%)	1(0.6%)	1 (0.6%)
		Rate per 100 PY	**0.6**	**0.6**
		95% CI	0.0, 3.4	0.0, 3.4
ASCEND-TD	2.9 (0.9, 5.0)	Events, n (%)	8 (3%)	0
		Rate per 100 PY	**2.9**	**0**
		95% CI	1.3, 5.8	0.0, 2.6
ASCEND-D	-0.3 (-0.8, 0.3)	Events, n (%)	43 (3%)	51 (3%)
		Rate per 100 PY	**1.2**	**1.5**
		95% CI	(0.9, 1.7)	1.1, 1.9



Principal Secondary Endpoint: MACE + TEE

n (%) ITT	ASCEND-ND			ASCEND-D		
	Daprodustat N = 1,937	Darbepoetin N = 1,935	HR (95% CI)	Daprodustat N = 1,487	ESA N = 1,477	HR (95% CI)
First occurrence MACE or thromboembolic events	422 **(21.8%)**	405 **(20.9%)**	**1.06** (0.93, 1.22)	497 **(33.4%)**	543 **(36.8%)**	**0.88** (0.78, 1.00)
MACE	363 (18.7%)	358 (18.5%)	-	326 (21.9%)	340 (23.0%)	-
Thromboembolic events	59 (3.0%)	47 (2.4%)	-	171 (11.5%)	203 (13.7%)	-

- Designed to allow assessment of risk for thromboembolic events or heart failure, inclusive of general CV risk
- Overcomes limitations and bias of competing risk when assessing endpoints individually

Thromboembolic events were adjudicated and include DVT, PE and vascular access thrombosis

Data on Thromboembolic Events

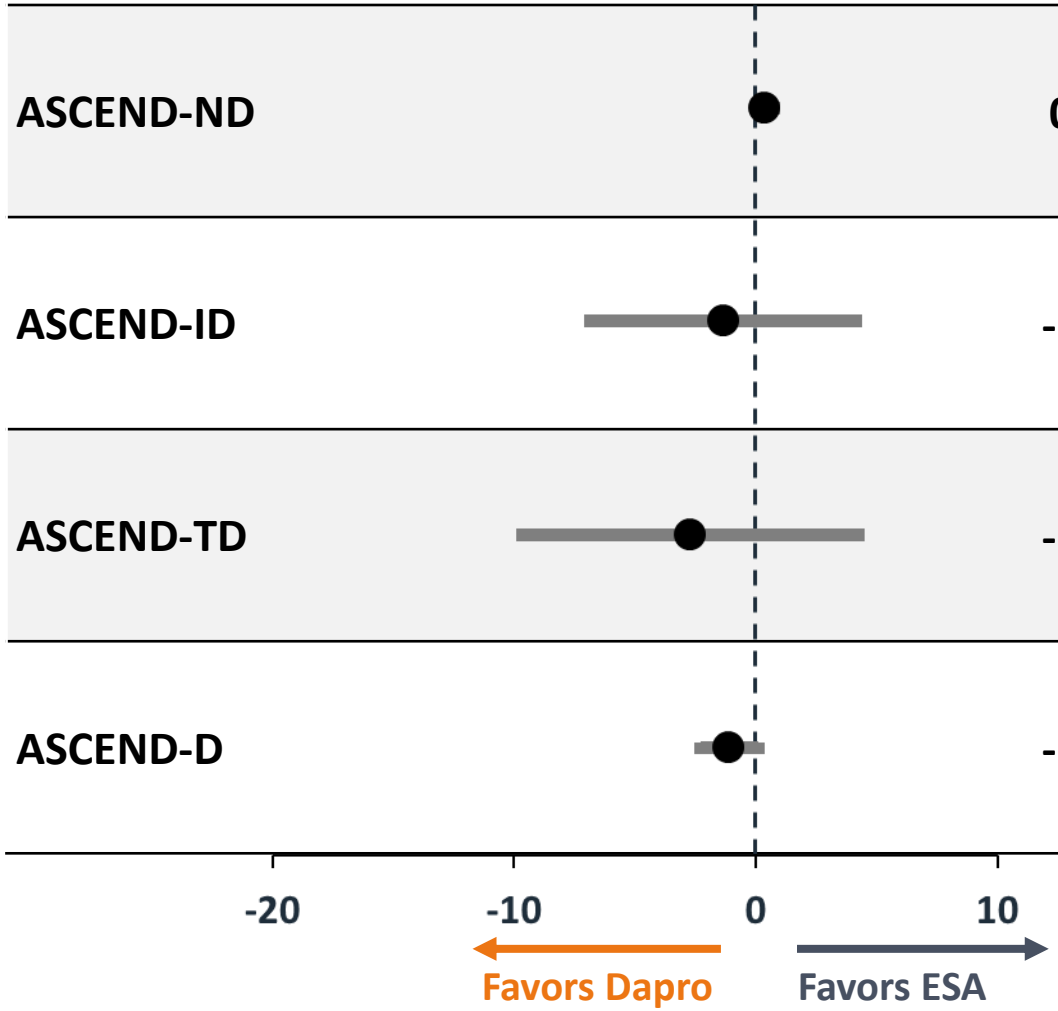
ITT	ASCEND-ND		ASCEND-D	
	Daprodustat N = 1,937	Darbepoetin N = 1,935	Daprodustat N = 1,487	ESA N = 1,477
Fatal and nonfatal thromboembolic events, n (%)				
First occurrence of thromboembolic events	64 **(3.3%)**	51 **(2.6%)**	185 **(12.4%)**	215 **(14.6%)**
Incidence rate per 100 PY (two-sided 95% CI)	**1.81** (1.39, 2.31)	**1.43** (1.07, 1.89)	**5.66** (4.87, 6.54)	**6.75** (5.88, 7.72)
Absolute rate difference per 100 PY (95% CI)	**0.37** (-0.22, 0.97)		**-1.09** (-2.31, 0.12)	
Hazard Ratio				
Estimate (two-sided 95% CI for HR)	**1.27** (0.88, 1.84)		**0.84** (0.69, 1.02)	

Adjudicated thromboembolic events comprised of deep vein thrombosis, pulmonary embolism and vascular access thrombosis.

Thromboembolic Events in ASCEND-ND and ASCEND-D

n (%) ITT	ASCEND-ND		ASCEND-D	
	Daprodustat N = 1,937	Darbepoetin N = 1,935	Daprodustat N = 1,487	ESA N = 1,477
First Occurrence thromboembolic event	64 **(3.3%)**	51 **(2.6%)**	185 **(12.4%)**	215 **(14.6%)**
Venous thromboembolism	20 **(1.0%)**	20 **(1.0%)**	23 **(1.5%)**	20 **(1.4%)**
Deep vein thrombosis	14 (0.7%)	19 (1.0%)	17 (1.1%)	14 (0.9%)
Pulmonary embolism	6 (0.3%)	1 (0.1%)	6 (0.4%)	6 (0.4%)
Fatal pulmonary embolism	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Vascular access thrombosis	44 **(2.3%)**	31 **(1.6%)**	162 **(10.9%)**	195 **(13.2%)**

Data on Thromboembolic Events Across ASCEND Program



	Dapro	ESA
Events, n (%)	64 (3.3%)	51 (2.6%)
Rate per 100 PY	**1.8**	**1.4**
95% CI	1.4, 2.3	1.1, 1.9
Events, n (%)	10 (6.4%)	12 (7.7%)
Rate per 100 PY	**6.2**	**7.6**
95% CI	3.0, 11.4	3.9, 13.2
Events, n (%)	27 (10.0%)	17 (12.4%)
Rate per 100 PY	**10.2**	**12.8**
95% CI	6.7, 14.8	7.5, 20.5
Events, n (%)	185 (12.4%)	215 (14.6%)
Rate per 100 PY	**5.7**	**6.8**
95% CI	4.9, 6.5	5.9, 7.7

Principal Secondary Endpoint: MACE + HHF

n (%) ITT	ASCEND-ND Daprodustat N = 1,937	ASCEND-ND Darbepoetin N = 1,935	ASCEND-ND HR (95% CI)	ASCEND-D Daprodustat N = 1,487	ASCEND-D ESA N = 1,477	ASCEND-D HR (95% CI)
First occurrence MACE or hospitalization for HF	444 **(22.9%)**	417 **(21.6%)**	**1.09** (0.95, 1.24)	425 **(28.6%)**	433 **(29.3%)**	**0.97** (0.85, 1.11)
Recurrent events*			**1.09** (0.93, 1.29)			**0.90** (0.76, 1.07)
MACE	337 (17.4%)	335 (17.3%)	-	340 (22.9%)	360 (24.4%)	-
Hospitalization for HF	107 (5.5%)	82 (4.2%)	-	85 (5.7%)	73 (4.9%)	-

*Post-hoc: rate ratio estimates based on a negative binomial model

Data on Hospitalization for Heart Failure

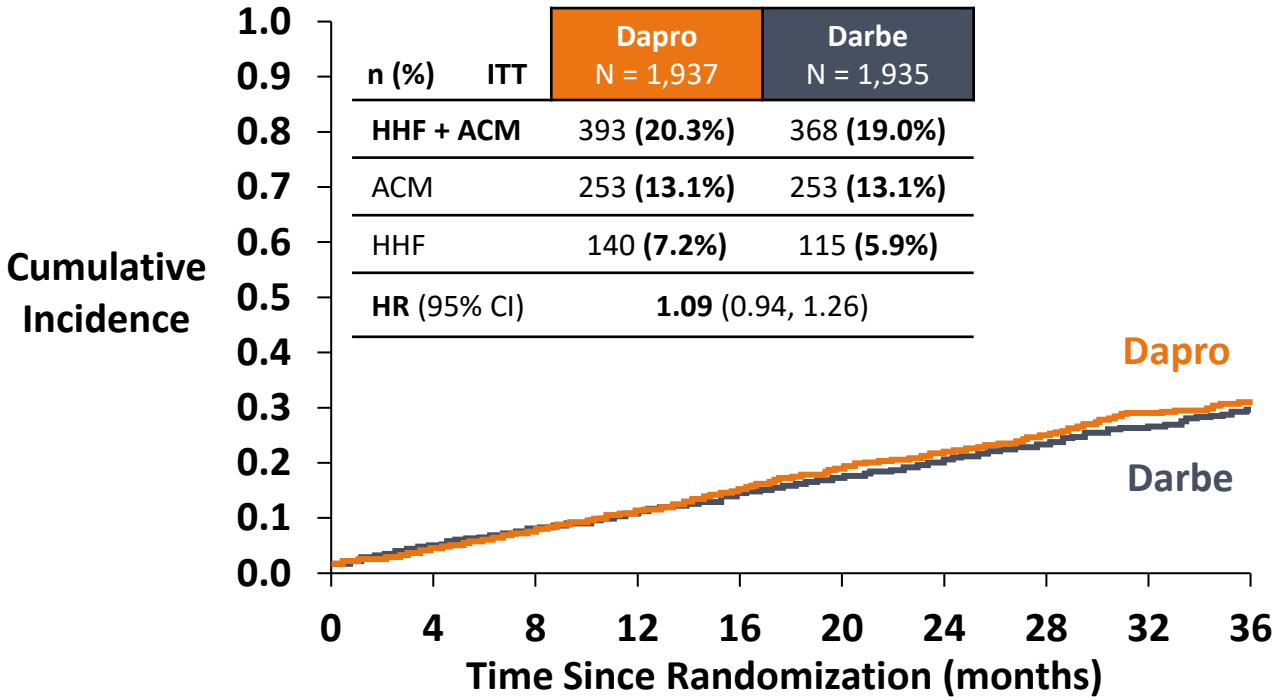
n (%) ITT	ASCEND-ND			ASCEND-D		
	Daprodustat N = 1,937	Darbepoetin N = 1,935	HR (95% CI)	Daprodustat N = 1,487	ESA N = 1,477	HR (95% CI)
Hospitalization for HF	140 **(7.2%)**	115 **(5.9%)**	**1.22** (0.95, 1.56)	112 **(7.5%)**	101 **(6.8%)**	**1.10** (0.84, 1.45)
Recurrent events*			**1.45** (1.09, 1.94)			**1.03** (0.76, 1.40)

*Post-hoc: rate ratio estimates based on a negative binomial model

Post-hoc: All-cause Mortality + HHF in ASCEND Program

ASCEND-ND

n (%) ITT	Dapro N = 1,937	Darbe N = 1,935
HHF + ACM	393 **(20.3%)**	368 **(19.0%)**
ACM	253 **(13.1%)**	253 **(13.1%)**
HHF	140 **(7.2%)**	115 **(5.9%)**
HR (95% CI)	**1.09** (0.94, 1.26)	

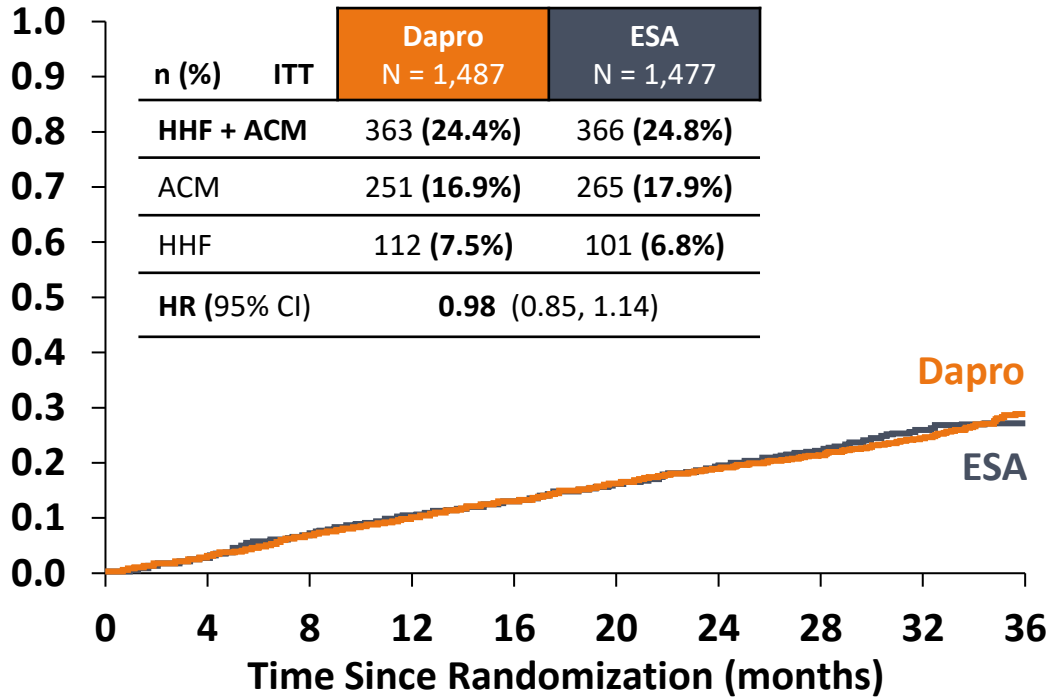


Patients at risk

Dapro	1937	1827	1593	1405	1196	1020	835	640	462	285
ESA	1935	1814	1568	1405	1218	1040	848	662	474	292

ASCEND-D

n (%) ITT	Dapro N = 1,487	ESA N = 1,477
HHF + ACM	363 **(24.4%)**	366 **(24.8%)**
ACM	251 **(16.9%)**	265 **(17.9%)**
HHF	112 **(7.5%)**	101 **(6.8%)**
HR (95% CI)	**0.98** (0.85, 1.14)	

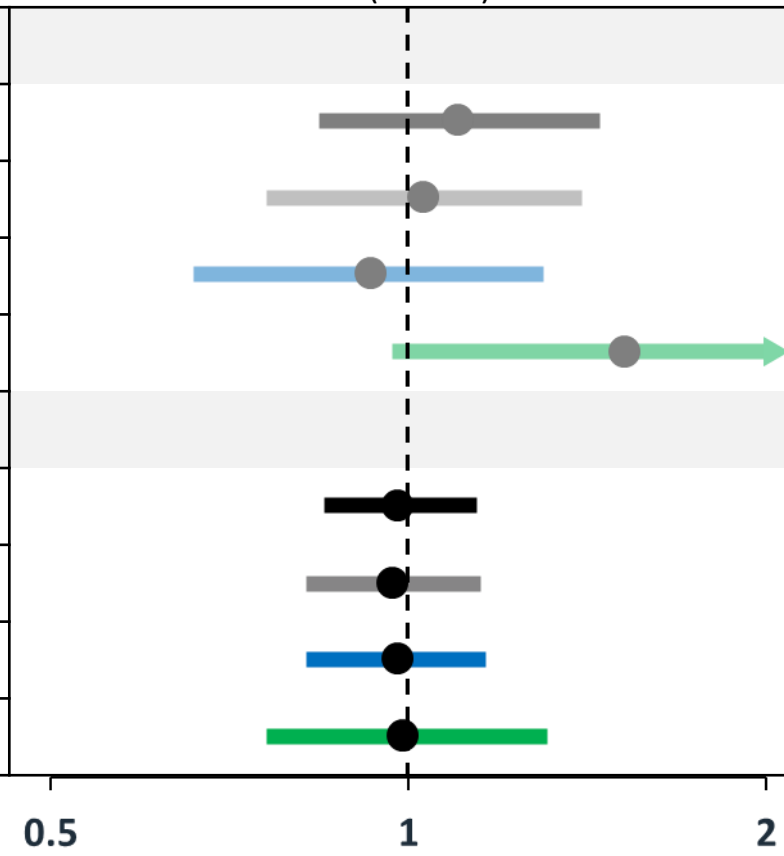


Dapro	1487	1433	1362	1300	1245	1190	1143	868	567	250
ESA	1477	1433	1352	1283	1234	1190	1130	853	535	255

ASCEND-D: Outcomes Overall and by Pre-existing Heart Failure

- **No increase in risk** of hospitalization for heart failure in ASCEND-D, when accounting for the competing risk of death:
  - Irrespective of prior history of heart failure

ITT	HR (95% CI)	HR (95% CI)
Hospitalization for heart failure		
Overall		**1.10** (0.84, 1.45)
Recurrent event analysis*		**1.03** (0.76, 1.40)
No history of heart failure		**0.93** (0.66, 1.30)
History of heart failure		**1.52** (0.97, 2.38)
ACM + Hospitalization for heart failure		
Overall		**0.98** (0.85, 1.14)
Recurrent event analysis*		**0.97** (0.82, 1.15)
No history of heart failure		**0.98** (0.82, 1.16)
History of heart failure		**0.99** (0.76, 1.31)



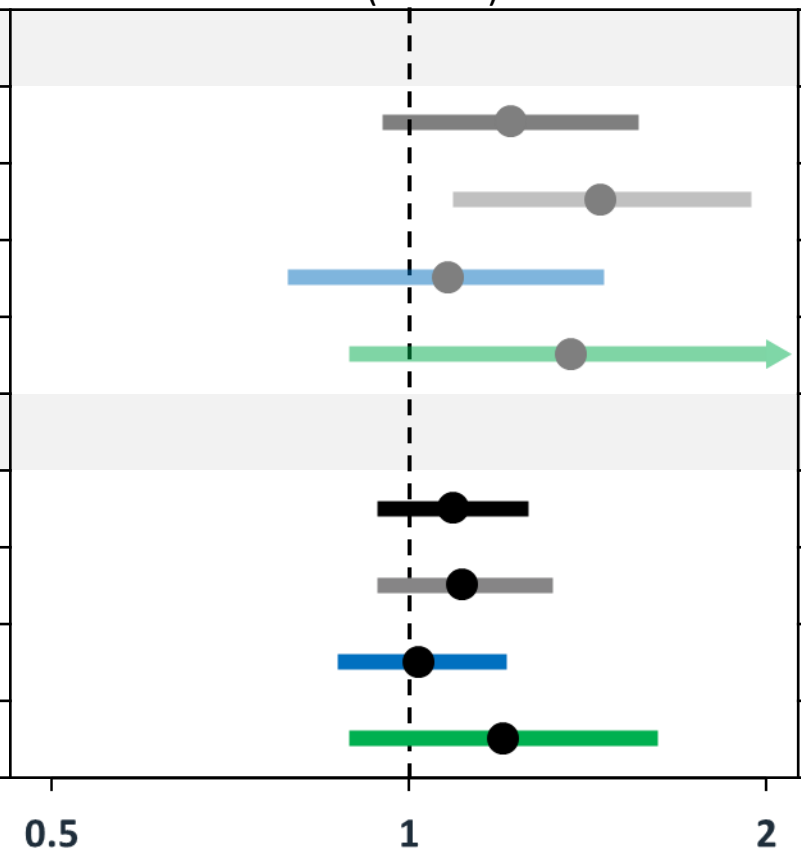
Post-hoc except for overall hospitalization for heart failure

*Rate ratio (not hazard ratio) reported for recurrent event analysis

ASCEND-ND: Outcomes Overall and by Pre-existing Heart Failure

- **No increase in incident heart failure** in patients without prior history of heart failure (87% of study population)
- **Increased incidence of worsening heart failure** in patients with a prior history of heart failure (13% of study population)

ITT	HR (95% CI)
Hospitalization for heart failure	
Overall	**1.22** (0.95, 1.56)
Recurrent event analysis*	**1.45** (1.09, 1.94)
No history of heart failure	**1.08** (0.79, 1.46)
History of heart failure	**1.37** (0.89, 2.11)
ACM + Hospitalization for heart failure	
Overall	**1.09** (0.94, 1.26)
Recurrent event analysis*	**1.11** (0.94, 1.32)
No history of heart failure	**1.02** (0.87, 1.21)
History of heart failure	**1.20** (0.89, 1.62)



Post-hoc except for overall Hosp for HF

*Rate ratio (not hazard ratio) reported for recurrent event analysis

ASCEND-ND: Outcomes in Those Without History of Heart Failure

ITT	HR (95% CI)	Dapro N = 1,671	Darbe N = 1,678
MACE	0.99 (0.84, 1.16)	286 (17.1%)	299 (17.8%)
ACM	0.99 (0.82, 1.18)	229 (13.7%)	241 (14.4%)
MI	0.97 (0.70, 1.35)	72 (4.3%)	75 (4.5%)
Stroke	1.20 (0.71, 2.02)	31 (1.9%)	26 (1.5%)
Hospitalization for HF	1.08 (0.79, 1.46)	86 (5.1%)	81 (4.8%)
ACM+HHF	1.02 (0.87, 1.21)	289 (17.3%)	292 (17.4%)
MACE+HHF	1.02 (0.88, 1.19)	331 (19.8%)	334 (19.9%)

Post-Hoc

Heart Failure Summary

- **Across both populations**, ASCEND trials supports no increased risk of incident heart failure, with additional supporting data from:
  - Absence of non-clinical findings for cardiac toxicity
  - Absence of adverse echo changes on LVEF in Phase 2 studies up to 24wks
  - Absence of plausible mechanism for direct myocardial injury

- **Dialysis**: No evidence of increased risk of ACM or HHF for daprodustat compared with ESA, irrespective of prior heart failure status

- **Non-dialysis patients <u>with</u> concomitant heart failure:** risk of worsening heart failure
  - History of heart failure subgroup may have contributed to broader CV outcomes: similar rates between treatment groups in those without history of heart failure

MACE: Analysis of ASCEND-ND On-Treatment Results Led to Further Investigation

ITT	ASCEND-ND		ASCEND-D	
	Daprodustat N = 1,937	Darbepoetin N = 1,935	Daprodustat N = 1,487	ESA N = 1,477
First occurrence of MACE	378 **(19.5%)**	371 **(19.2%)**	374 **(25.2%)**	394 **(26.7%)**
HR (95% CI)	**1.03** (0.89, 1.19)		**0.93** (0.81, 1.07)	

Pre-Specified On-Treatment (LDD + 28 days)

Supportive On-Treatment Analyses, n (%)	ASCEND-ND		ASCEND-D	
	Daprodustat N = 1,937	Darbepoetin N = 1,935	Daprodustat N = 1,487	ESA N = 1,477
Analysis of time to first occurrence of MACE, n	**1,937**	**1,933**	**1,482**	**1,474**
First occurrence of on treatment adjudicated MACE	274 **(14.1%)**	202 **(10.5%)**	255 **(17.2%)**	271 **(18.4%)**
Adjusted HR (95% CI)	**1.40** (1.17, 1.68)		**0.96** (0.81, 1.14)	

Differential Dosing Frequency & On-Treatment Analysis Bias

Kevin J Carroll, PhD

Chief Statistician

KJC Statistics Ltd.

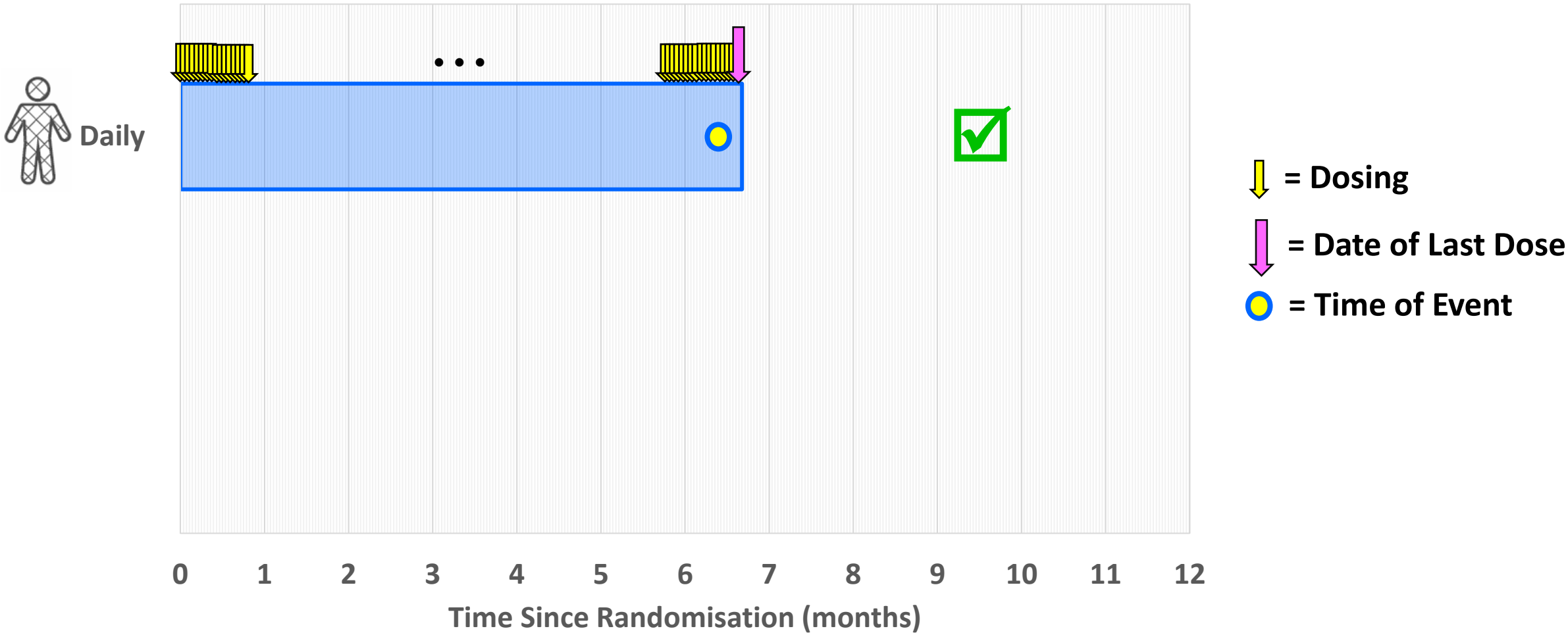
ASCEND Executive Steering Committee Member

‘On-Treatment’ Analyses When DF Differs Between Arms

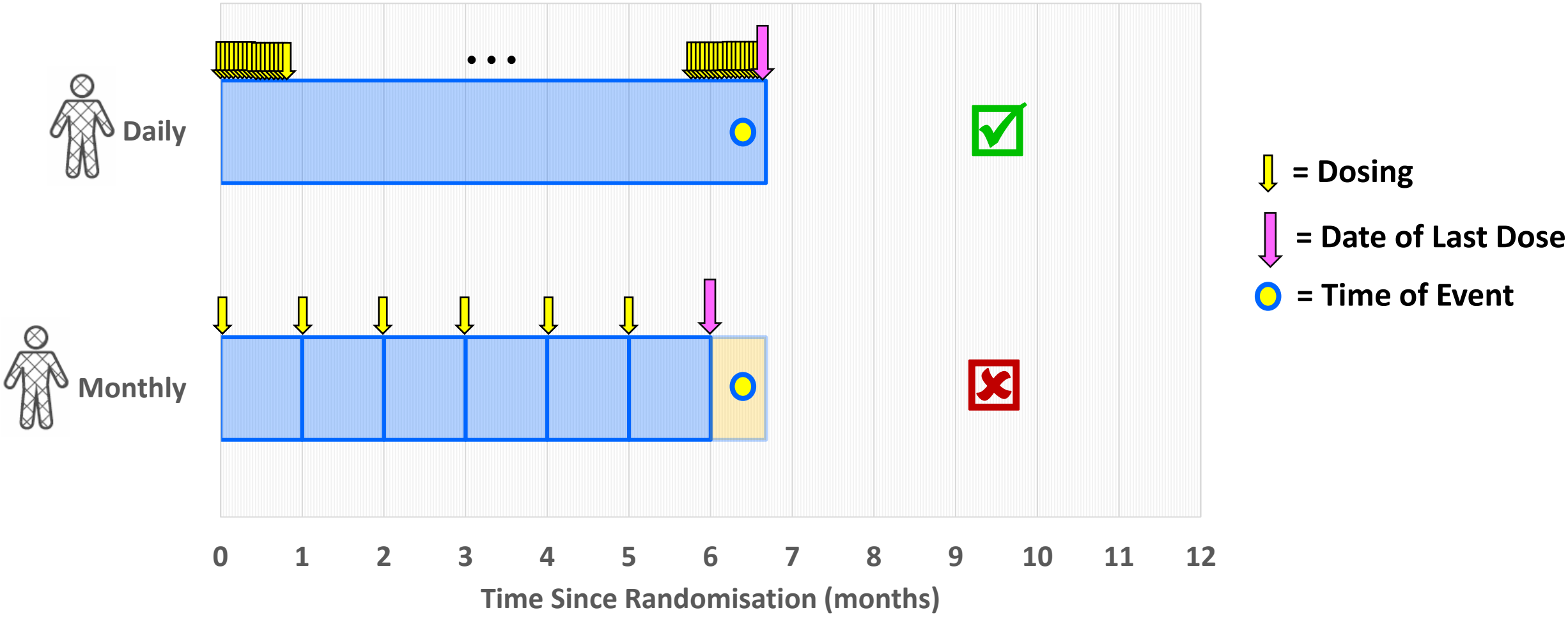
- Primary ITT analyses, agreed with FDA, respect randomization and provide the best reflection of the effect of a treatment policy
- ‘On-Treatment’ analyses planned to supplement ITT Primary Analysis
  - Pre-specified on-treatment definition: Last dose date + 28 days
- However, differential dosing frequency can introduce substantial bias if not accounted for in the analysis

DeMets, 2019; Greenland, 2008, Granger, 2005; Yang, 2019

‘On Treatment’ Events : Daily vs Monthly Dosing



‘On Treatment’ Events : Daily vs Monthly Dosing



Possible Approaches to Address the Bias

- Redefine ‘On-Treatment’ as date of last dose **+ Dosing Frequency**
  - Dosing Frequency = 1, 2 or 4 weeks for Darbe
  - Dosing Frequency = 1 day for Dapro
  - Effective in reducing bias
- Use the **Date of Decision to Stop Dosing**
  - CRF collected Date of Decision to Stop Dosing
  - For Darbe, this can be considered as a substitute for what the date of last dose might have been if dosing had been daily
  - Effective in reducing bias

MACE First 'On-Treatment' Event Analyses in ASCEND-ND Corrected Definition For Differential Dosing Frequency

ITT Events on / after randomization	Pre-Specified On-Treatment Last dose date + 28d
HR (95% CI) 1.03 (0.89, 1.19) Events 378 v 371	HR (95% CI) 1.40 (1.17, 1.68) Events 274 v 202

Post-Hoc On-Treatment Last dose date + DF	Post-Hoc On-Treatment Last dose date + DF + 28d	Post-Hoc On-Treatment Date of Decision to Stop	Post-Hoc On-Treatment Date Decision to Stop + 28d
HR (95% CI) 1.09 (0.89, 1.33) Events 192 v 189	HR (95% CI) 1.18 (0.99, 1.40) Events 275 v 248	HR (95% CI) 1.06 (0.89, 1.27) Events 246 v 240	HR (95% CI) 1.16 (0.99, 1.37) Events 302 v 268

Summary

- All ‘On-Treatment’ analyses carry a common set of issues and biases
- No allowance for differential dosing frequency can seriously bias ‘On-Treatment’ analyses
- Pre-planned ‘On-Treatment’ analyses in ASCEND program did not account for differential dosing frequency
- Correction for differential dosing frequency provides results more in keeping with Primary ITT analysis

General Safety

Heather Stein, MD, MPH

Vice President, Safety Evaluation and Risk Management

Global Safety

GSK

Evaluation of Esophageal and Gastric Erosions in the Cardiovascular Outcomes Trials

LDD + DF Esophageal and gastric erosions AESI by preferred term, n (%)	ASCEND-ND		ASCEND-D	
	Dapro N = 1,937	Darbe N = 1,933	Dapro N = 1,482	ESA N = 1,474
GI hemorrhage	20 **(1.0%)**	9 **(0.5%)**	16 **(1.1%)**	22 **(1.5%)**
Gastritis erosive	14 **(0.7%)**	8 **(0.4%)**	14 **(0.9%)**	14 **(0.9%)**
Upper GI hemorrhage	14 **(0.7%)**	10 **(0.5%)**	4 **(0.3%)**	6 **(0.4%)**
Gastric ulcer	4 **(0.2%)**	6 **(0.3%)**	7 **(0.5%)**	12 **(0.8%)**

AEs in the AESI of esophageal and gastric erosions occurring in ≥ 10 patients in any treatment group

Imbalance in Gastric Erosions/GI Hemorrhage Seen in Opposite Directions in the Cardiovascular Outcomes Trials

LDD + DF	ASCEND-ND Dapro N = 1,937	ASCEND-ND Darbe N = 1,933	ASCEND-ND Relative Risk (95% CI)	ASCEND-D Dapro N = 1,482	ASCEND-D ESA N = 1,474	ASCEND-D Relative Risk (95% CI)
AESI gastric erosion/GI hemorrhage, n (%)	70 **(3.6%)**	48 **(2.5%)**	**1.46** (1.01, 2.09)	60 **(4.0%)**	82 **(5.6%)**	**0.73** (0.53, 1.01)
Serious AESI gastric erosion/GI hemorrhage, n (%) (GSK definition)	39 **(2.0%)**	23 **(1.2%)**	**1.79*** (1.07, 3.00)	38 **(2.6%)**	34 **(2.3%)**	**1.15*** (0.72, 1.82)
Serious AESI gastric erosion/GI hemorrhage, n (%) (FDA definition)	47 **(2.4%)**	31 **(1.6%)**	**1.61*** (1.02, 2.53)	44 **(3.0%)**	44 **(3.0%)**	**1.03*** (0.68, 1.57)

*Hazard Ratio

Totality of Data Does Not Support an Increased Risk for Gastric Erosions/GI Hemorrhage Relative to ESAs

Gastric erosion/GI hemorrhage (LDD+DF)	ASCEND-NHQ		ASCEND-ND*		ASCEND-D*	
	Dapro N = 308	Placebo N = 306	Dapro N = 1,937	Darbe N = 1,933	Dapro N = 1,482	ESA N = 1,474
Patients with event, n (%)	2 (0.6%)	3 (1.0%)	70 (3.6%)	48 (2.5%)	60 (4.0%)	82 (5.6%)
Of the patients with AESI of gastric erosion (GSK definition), n (%)						
Drug-related	0	0	0	1 (2.1%)	0	0
Continued treatment	1 (50.0%)	2 (66.7%)	60 (85.7%)	38 (79.2%)	53 (88.3%)	76 (92.7%)
Resolved/resolving	2 (100.0%)	2 (66.7%)	54 (77.1%)	33 (68.8%)	43 (71.7%)	57 (69.5%)

Expert Review Conclusion: "In light of the fact that no difference was seen in confirmed clinically significant disease without another documented cause in ASCEND D, the difference in ASCEND ND could be due to the play of chance or represent a true difference between study groups in the risk of erosive disease in this study population."

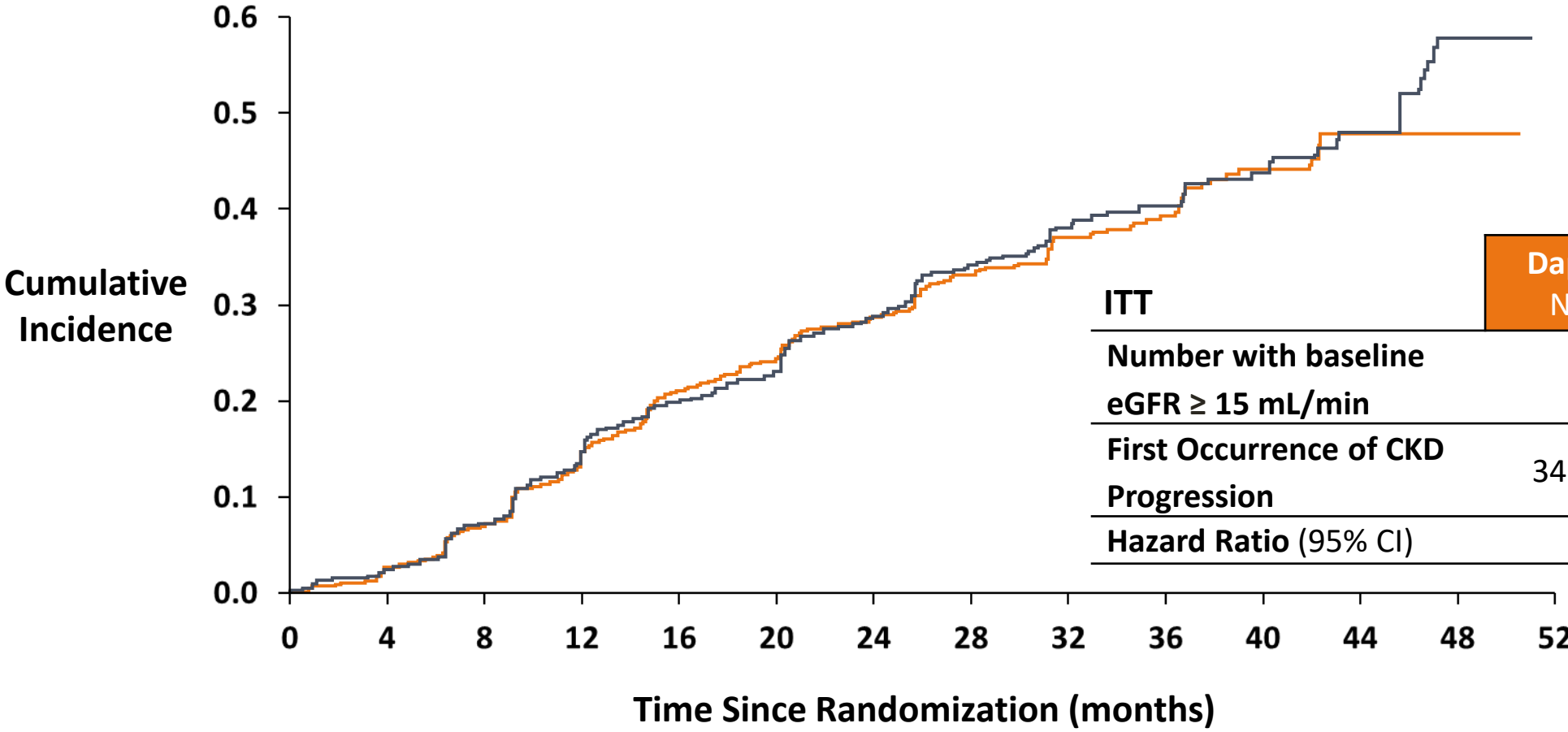
*Post-hoc

Acute Kidney Injury

ASCEND-ND: Post-hoc Analyses of Serious AKI (FDA Definition)

Time Period	Dapro N = 1,937	Darbe N = 1,933	**HR** (95% CI)
OT (LDD+DF)	**77 (4.0)**	**56 (2.9)**	**1.45** (1.03, 2.05)
AKI	70	50	
Anuria	0	1	
Cardiorenal syndrome	2	2	
Oliguria	1	0	
Renal tubular necrosis	1	0	
Tubulointerstitial nephritis	1	2	
Nephropathy toxic	2	1	
mITT, on and off treatment	**94 (4.9)**	**64 (3.3)**	**1.48** (1.08, 2.03)

ASCEND-ND: No Difference in Time to First Occurrence of CKD Progression

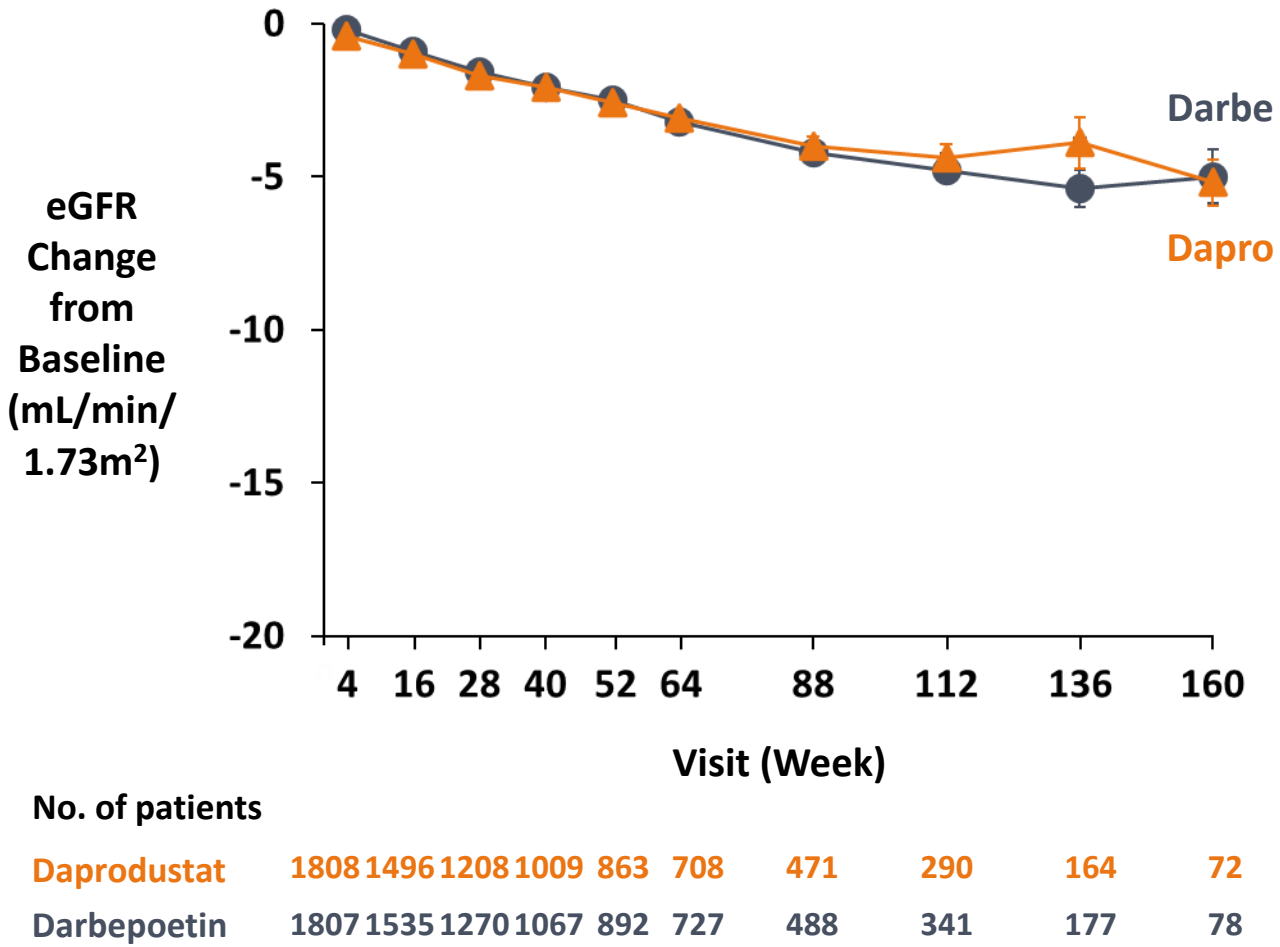


ITT	Daprodustat N = 1,937	Darbepoetin N = 1,935
Number with baseline eGFR ≥ 15 mL/min	**1,220**	**1,265**
First Occurrence of CKD Progression	343 **(28.1%)**	359 **(28.4%)**
Hazard Ratio (95% CI)	**0.98** (0.84, 1.13)	

Patients at risk

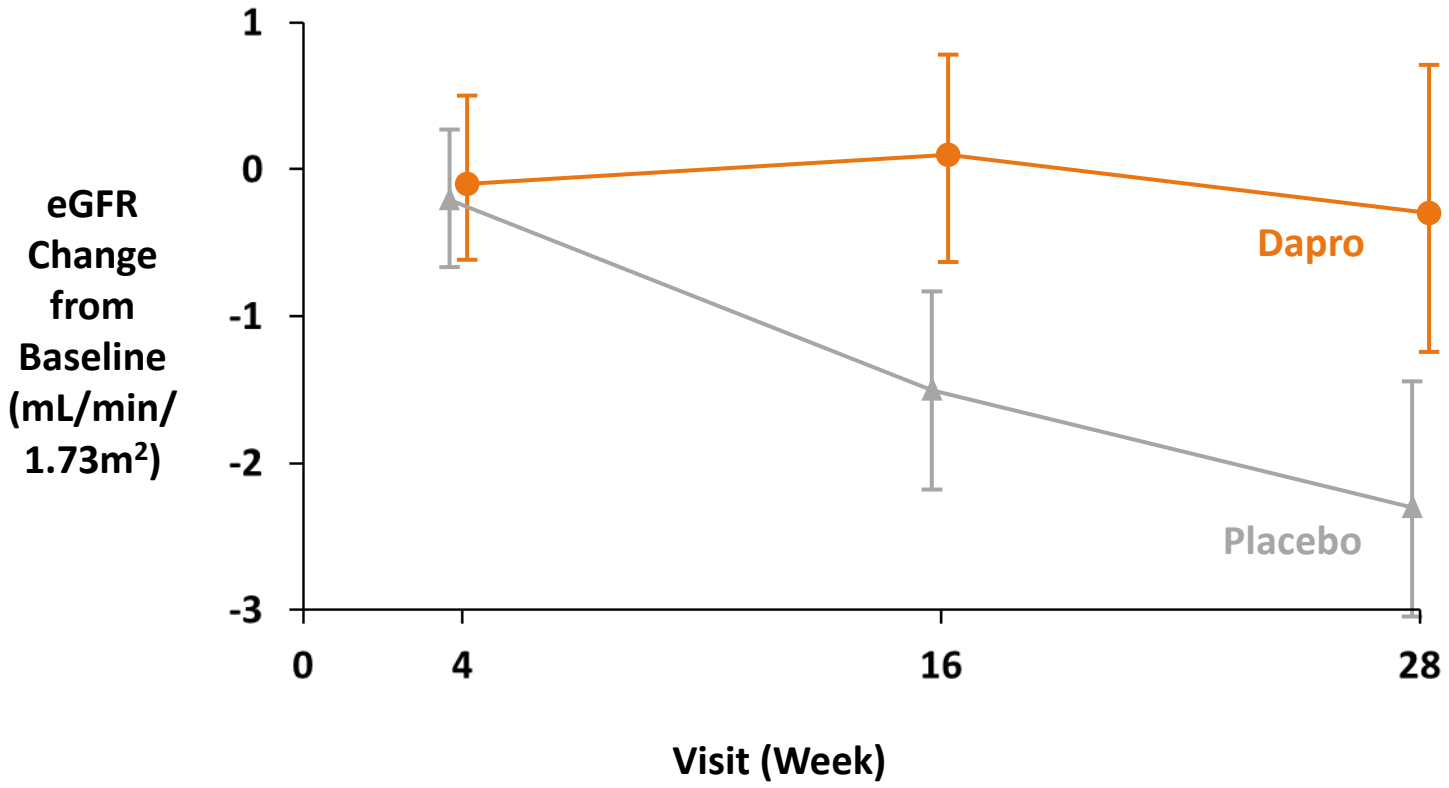
Dapro	1220	1148	966	804	642	535	427	313	211	136	59	14	2	0
Darbe	1265	1188	994	828	684	570	434	316	224	128	63	21	4	0

ASCEND-ND: Decline in On-Treatment eGFR Similar Between Treatment Groups



	Dapro N = 1,937	Darbe N = 1,933
eGFR (ml/min/1.73m²) change from baseline category, n	1867	1854
To low (any ≥ 40% decline in eGFR)	482 **(26%)**	480 **(26%)**
Within range or no change	1385 **(74%)**	1374 **(74%)**

ASCEND-NHQ: On-Treatment eGFR Decline Less with Daprodustat than Placebo



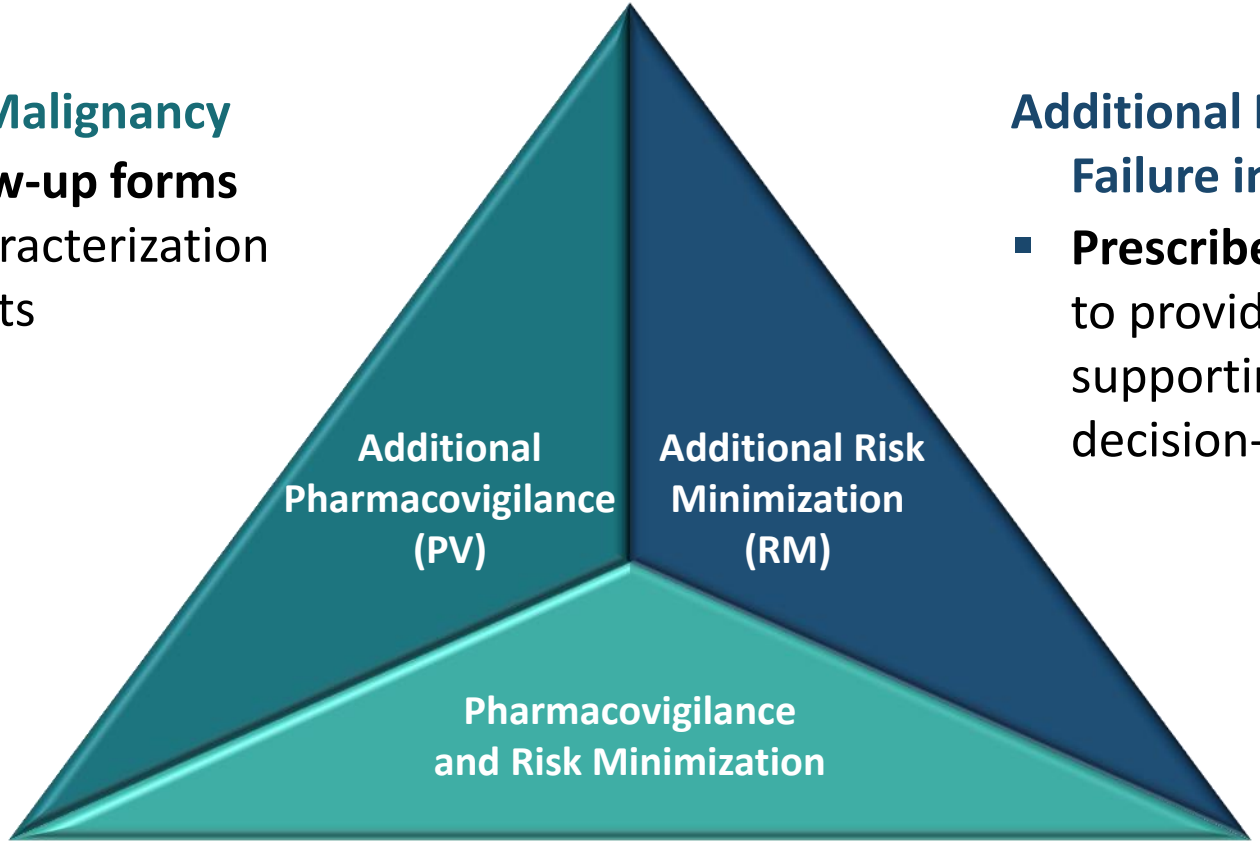
No. of patients			
Daprodustat	283	261	244
Placebo	283	235	211

	Daprodustat N = 244	Placebo N = 211
Mean eGFR decline after 28 weeks (mL/min/1.73m)	-0.3	-2.3

Proposed Proactive Pharmacovigilance and Risk Management in the Post-Marketing Setting

Additional PV for Malignancy

- **Targeted follow-up forms** for further characterization of cancer events



Additional RM for Risk of Heart Failure in ND Patients

- **Prescriber Education Materials** to provide additional information supporting individual benefit/risk decision-making

Pharmacovigilance

- In-stream review of individual case safety reports
- Monthly signal detection
- Regular literature review

Risk Minimization

- Labelling
  - Warnings & Precautions
  - Adverse Drug Reactions

Daprodustat Has Similar CV Safety as ESAs and an Acceptable General Safety Profile

- Placebo-controlled study: daprodustat well tolerated; no differences in MACE
- Both CVOTs met co-primary safety endpoint: Risk of MACE non-inferior to ESAs
- Risk of hospitalization for heart failure appears to be increased in non-dialysis patients with a history of heart failure
  - Risk mitigation proposal: labeling and prescriber education materials
- Most frequently reported AEs were common events of target populations
- No increased risk of malignancy, gastric erosions/GI hemorrhage, or AKI
- Safety issues with other HIF-PHIs not observed with daprodustat, including DILI
- Benefit/risk is favorable for both ND and D patients

Clinical Perspective

Ajay Singh, MBBS, FRCP (UK), MBA

ASCEND Executive Steering Committee Chair

Senior Associate Dean for Postgraduate Medical Education

Director, Master in Medical Sciences in Clinical Investigation Program

Harvard Medical School

Physician, Renal Division, Brigham and Women’s Hospital

Unmet Need Exists in Non-Dialysis Dialysis Patients with Anemia of CKD

- Clinic-based therapies for ND and home therapy patients are challenging and represent a bottleneck
  - Challenging logistics
  - Disparities in accessing anemia therapy
- Home dialysis (Peritoneal dialysis (~11% of patients)
  - Rural patients may be hours from dialysis center
  - National initiatives focused on increasing home dialysis

Not Treating Anemia of CKD Has Risks

- Risk of transfusion
  - Allosensitization & impact on transplant availability
  - Risk of acute volume overload and hyperkalemia
  - AEs of liberal blood transfusion
  - Infection
- Reduced health-related quality of life

ASCEND Program Summary

- Well-designed and well-conducted study
  - Rigorous follow up and internal validity
  - Representative patient population
- Efficacy for daprodustat in both the D and ND population isn't being debated
- The FDA raised important concerns in the ND population
  - On Treatment MACE
  - US versus non-US
  - The CV endpoint analysis
  - Heart Failure
  - AKI
  - GI erosions

ASCEND Trials Demonstrated Favorable Benefit-Risk Assessment for Daprodustat

- Convenient and flexible treatment option
- Important advance for dialysis and non-dialysis patients
- Additional tool for nephrologists to effectively care for patients
- Similar efficacy and a safety profile comparable to ESA in the pre-specified ITT population for both D and ND CKD patients

Daprodustat could represent an oral alternative to ESA for treating patients across the spectrum of anemia of CKD

Daprodustat for the Treatment of Anemia of Chronic Kidney Disease

October 26, 2022

GSK

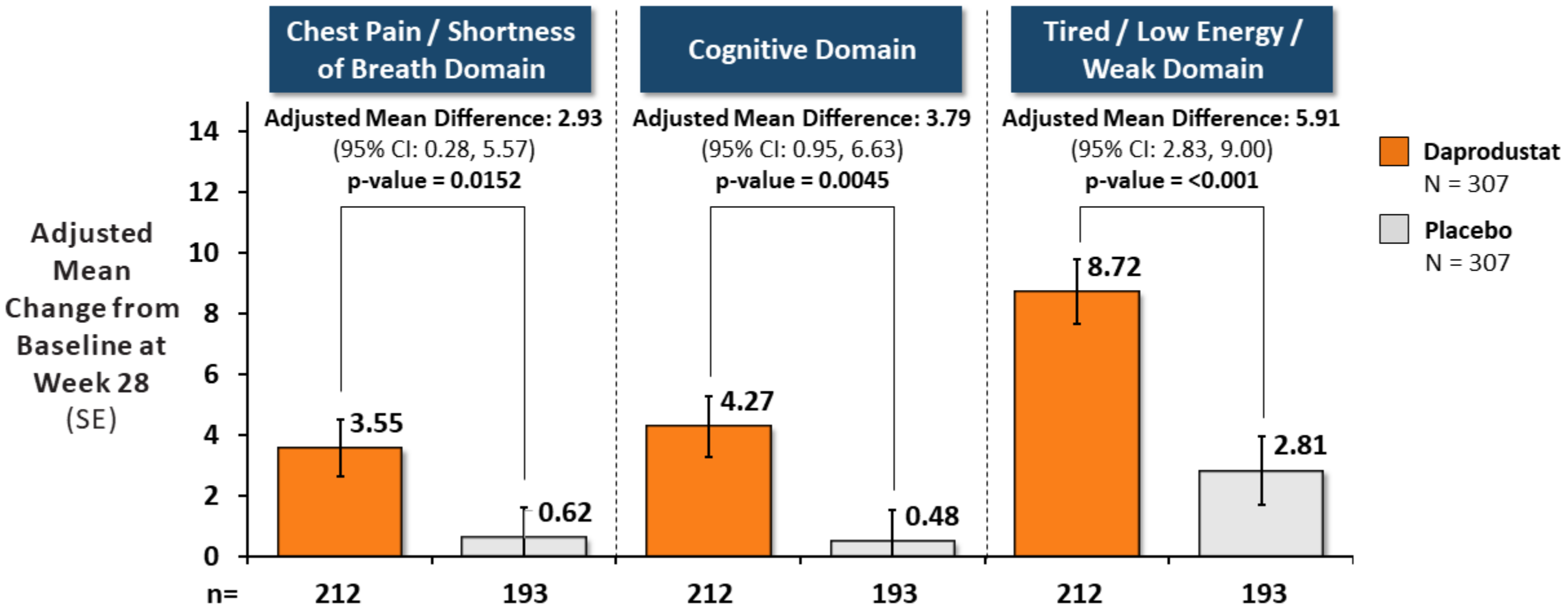
Cardiovascular and Renal Drugs Advisory Committee

Gastrointestinal Hemorrhage in the Cardiovascular Outcomes Trials

LDD + DF GI Hemorrhage SMQ, n (%)	ASCEND-ND		ASCEND-D	
	Dapro N = 1,937	Darbe N = 1,933	Dapro N = 1,482	ESA N = 1,474
Any event	62 (3%)	55 (3%)	69 (5%)	77 (5%)
GI hemorrhage	20 (1%)	9 (<1%)	16 (1%)	22 (1%)
Upper GI hemorrhage	14 (<1%)	10 (<1%)	4 (<1%)	6 (<1%)
Rectal hemorrhage	7 (<1%)	8 (<1%)	4 (<1%)	10 (<1%)
Hematochezia	5 (<1%)	3 (<1%)	10 (<1%)	10 (<1%)
Hemorrhoidal hemorrhage	2 (<1%)	3 (<1%)	13 (<1%)	8 (<1%)
Any serious event	36 (2%)	32 (2%)	34 (2%)	31 (2%)
GI hemorrhage	12 (<1%)	7 (<1%)	12 (<1%)	12 (<1%)
Upper GI hemorrhage	12 (<1%)	7 (<1%)	4 (<1%)	4 (<1%)

AEs in the GI Hemorrhage SMQ in ≥ 10 patients in any treatment group
Post-hoc, Safety Population

The CKD-AQ Provides Supportive Evidence Showing the Impact of Dapro on QoL: ASCEND-NHQ



On-treatment analysis

CKD-AQ = Chronic Kidney Disease Anemia Symptoms Questionnaire

ASCEND-ND: Summary of Concordance Between Investigator Reported and Adjudicated MACE During Time Period for Follow-Up of CV Events

	Investigator-Reported Event Type Treatment Total N = 3,872		
Adjudicated Event Type	MACE[a]	Not MACE[b]	No Reported Event[c]
MACE	790	146	2
Not MACE	101	491	0
Did not meet criteria[d]	1	1	0
Cases sent for adjudication	892	638	2
Concordance	84%		

a. Investigator-reported MACE includes all investigator-reported death, MI and stroke (primary ischemic stroke, primary intracranial hemorrhage, retinal/ocular hemorrhage or infarction, unknown type of stroke) events.
b. Investigator-reported not MACE incudes unstable angina, non-ischemic chest pain, transient ischemic attack, and referred MI and stroke events deemed not an endpoint by the investigator
c. Event was manually triggered by the CEC
d. CEC determined that the event did not meet criteria for adjudication

Characterization of Worsening Heart Failure

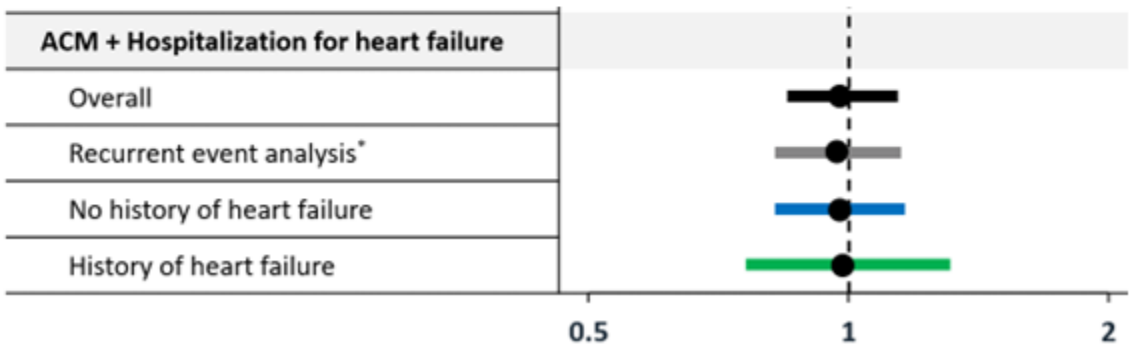
More adjudicated events determined by PI as fluid overload (rather than HF)

Dapro 45/140 (32%) vs. Darbe 29/115 (25%)

More dialysis initiation in cohort with Hospitalization for HF across treatment arms

ITT population ~1/3 vs. HHF cohort ~2/3

No risk observed in ASCEND-D (HRs <1)



No increase in Mortality despite higher number of HHF in daprodustat arm

Dapro 47/140 (33.6%) vs. Darbe 45/115 (39.1%)

Post-hoc

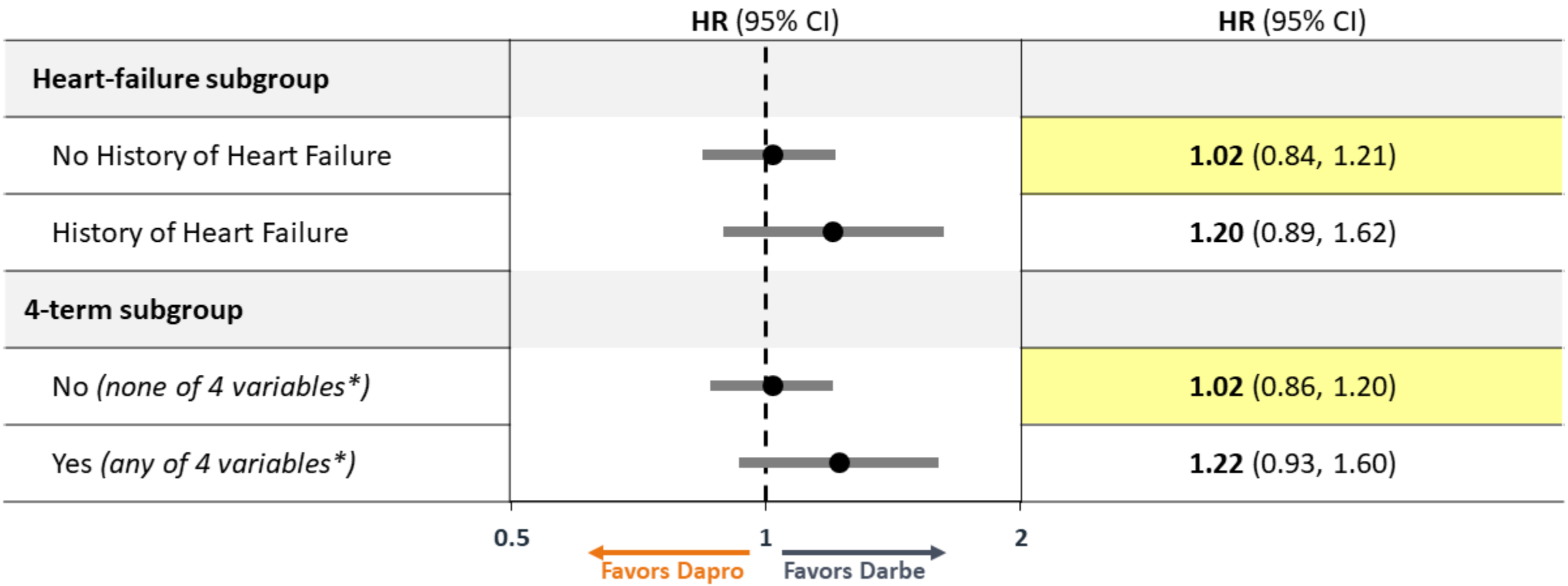
MACE and Principal Secondary by US vs Non-US Region

ASCEND-ND adjusted for baseline covariates

		ASCEND-ND*				ASCEND-D			
		Dapro	Darbe	Hazard Ratio (95% CI)	p-value	Dapro	ESA	Hazard Ratio (95% CI)	p-value
MACE	US	24%	21%	**1.10** (0.84, 1.43)	**0.3789**	32%	33%	**0.96** (0.76, 1.21)	**0.7905**
	Non-US	18%	18%	**0.95** (0.80, 1.13)		22%	24%	**0.92** (0.77, 1.10)	
MACE + thromboembolic event	US	28%	23%	**1.15** (0.90, 1.48)	**0.2163**	41%	43%	**0.93** (0.75, 1.14)	**0.6116**
	Non-US	20%	20%	**0.95** (0.81, 1.12)		30%	34%	**0.87** (0.75, 1.01)	
MACE + Hospitalization for heart failure	US	29%	24%	**1.18** (0.92, 1.51)	**0.2555**	38%	37%	**1.03** (0.82, 1.28)	**0.5344**
	Non-US	21%	21%	**1.00** (0.85, 1.17)		25%	26%	**0.94** (0.79, 1.11)	

***model adjusted for baseline eGFR and Baseline History of Heart Failure; model for MACE+TEE is also adjusted for history of VTE, age >=75 years, and vascular access at randomization**

ASCEND-ND: All-cause Mortality + HHF in ASCEND-ND: Screening Cardiac Subgroup vs. History of Heart (4-term Definition)



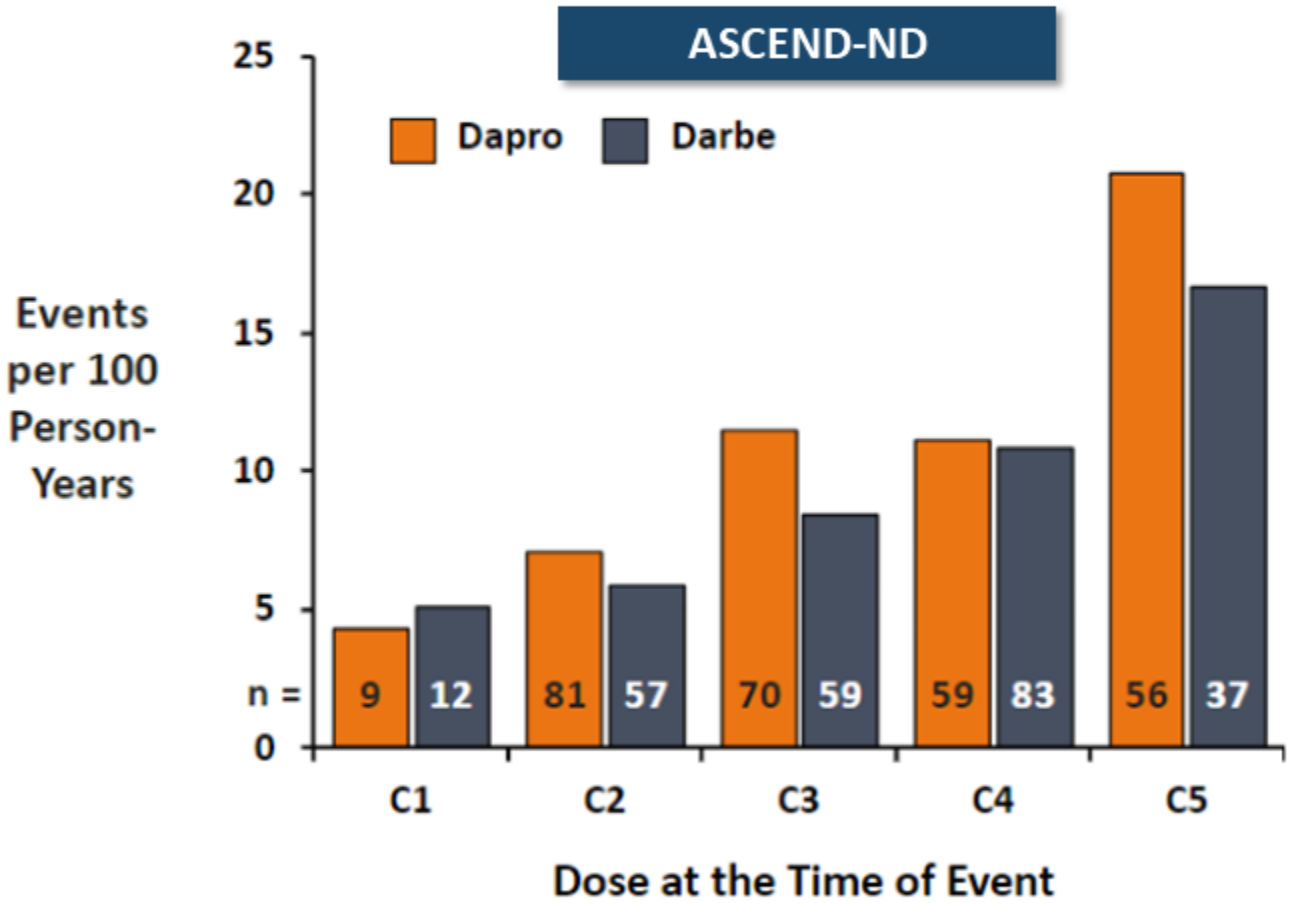
- **83-89% of events in the 4-term definition were derived from those with heart failure**, irrespective of the presence of the other 3 medical history terms

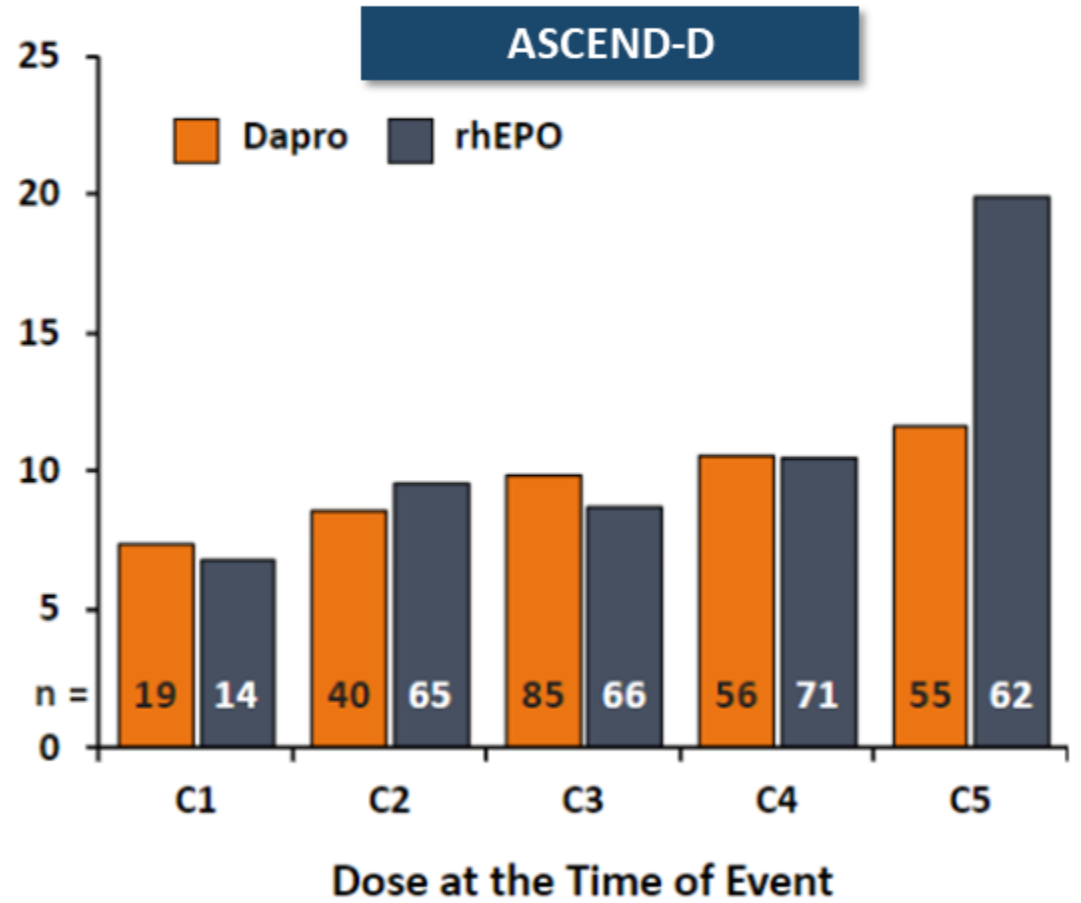
*4-term subgroup was pre-specified to include any of: pulmonary hypertension; left ventricular systolic dysfunction; left ventricular disastolic dysfunction; heart failure

MACE by Dose Categories Based on the Dose at the Time of the Event (Events per 100 Person-Years)

On-treatment; Adjusted for Dosing Frequency

QU-5





Dosing categories

Dapro	0 mg	0 to 28 mg	28 to 42 mg	42 to 70 mg	≥70 mg
ESA	0 µg	0 to 15 µg	15 to 25 µg	25 o 75 µg	≥75 µg

Dapro	0 mg	0 to 28 mg	28 to 56 mg	56 to 84 mg	≥84 mg
ESA	0 U	0 to 5000 U	5000 to 10000 U	10000 to 18000 U	≥18000 U

Post-hoc