New Drug Application 216951
Daprodustat oral tablets

FDA Opening Remarks

Cardiovascular and Renal Drugs Advisory Committee Meeting
October 26, 2022

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Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration

Daprodustat

- Proposed Indication: Treatment of anemia due to chronic kidney disease (CKD) in adults on dialysis and not on dialysis
- Dosing: Oral
- Mechanism of Action (under review):
  - Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor
  - Promotes stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors
  - Leads to increased transcription of the HIF-responsive genes, including erythropoietin and transferrin

Treatment of Anemia Due to CKD

- Erythropoiesis stimulating agents (ESAs) administered intravenously or by subcutaneous injection
- Revisions to the approved ESA labeling
  - Boxed Warning for increased mortality and serious cardiovascular and thromboembolic events
  - Dosing and administration section includes
    - A reduction in the recommended "target" hemoglobin (Hb)
    - A recommendation to discontinue if Hb does not respond adequately over a 12-week dose-escalation period

Development Program for Treatment of Anemia Due to CKD

- Development for HIF-PHI predicated on ESAs
- All trials of new agents for anemia of CKD must
  - Achieve similar “target” Hb as the ESA comparator
  - Include a prespecified analysis of Major Adverse Cardiac Events (MACE) – composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke

Daprodustat Development Program

- Two similar event-driven, international, open-label, randomized, parallel-group trials in different CKD populations
  - ASCEND-ND (patients not on dialysis)
  - ASCEND-D (patients on dialysis)
- Both trials compared daprodustat to ESA
- Two co-primary endpoints (non-inferiority hypothesis tested)
  - Efficacy: mean change in Hb from baseline over weeks 28 to 52
  - Safety: time to first occurrence of adjudicated MACE

Trials' Primary Results

- Non-inferiority of daprodustat to ESA established for the two co-primary endpoints for each trial.

Daprodustat Risks

- ASCEND-ND
  - Elevated estimated hazard ratios (HRs) for
    - Myocardial infarction
    - Stroke
    - Thromboembolism, including vascular access thrombosis
    - Acute kidney injury
    - Hospitalization for heart failure
    - Gastrointestinal erosions/bleeding
  - U.S. subgroup had higher HR estimates for cardiovascular endpoints (except stroke) than the non-U.S. subgroup

Daprodustat Risks

- ASCEND-D
  - Elevated estimated HRs for
    - Hospitalization for heart failure
    - Gastrointestinal erosions/bleeding

Summary of Benefits and Risks (1)

- Efficacy:
  - Noninferior to ESA on Hb change
  - Similar rate of red blood cell transfusions
  - No other meaningful benefits established

Summary of Benefits and Risks (2)

- Safety – noninferior on MACE **but no superiority demonstrated to the ESAs** which have
  - Boxed Warning for increased mortality and serious cardiovascular and thromboembolic events.
  - Warnings for hypertension, seizures, and thrombotic events including vascular access thromboses.
  - Recommended "target" Hb and a recommendation to discontinue the ESA if inadequate response.
- **Secondary and exploratory safety analyses suggest potential for increased risks with daprodustat compared to ESA, particularly for the non-dialysis population and U.S. subgroup.**

Summary of Benefits and Risks (3)

- Oral formulation may provide convenience but…
  - Usefulness is less clear for hemodialysis population
  - Potential for increased harm in the U.S. subgroup and non-dialysis population
  - Safety monitoring may be more challenging for patients who may not be seen frequently
    - Peritoneal dialysis population
    - Non-dialysis population

Discussion and Voting Questions

Discussion Questions

1. Discuss the benefits of daprodustat in adults with non-dialysis dependent (NDD) chronic kidney disease (CKD).

2. Discuss the benefits of daprodustat in adults with dialysis dependent (DD) CKD.

3. Discuss the risks of daprodustat in adults with NDD CKD, including cardiovascular harm, gastrointestinal erosions/hemorrhage, and acute kidney injury.

4. Discuss the risks of daprodustat in adults with DD CKD, including the risks of heart failure and gastrointestinal erosions/hemorrhage.

Voting Questions

5. Do the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults not on dialysis?
   - Provide rationale for your vote.
   - If you voted No, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment.

6. Do the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults on dialysis?
   - Provide rationale for your vote.
   - If you voted No, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment.


FDA
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ADMINISTRATION

Background and Efficacy of Daprodustat

Cardiovascular and Renal Drugs Advisory Committee Meeting
October 26, 2022

Justin Penzenstadler, PharmD
Clinical Reviewer
Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Center for Drug Evaluation and Research (CDER), FDA

Daprodustat Review Team

- Clinical
  - Justin Penzenstadler
  - Patricia Oneal
  - Tanya Wroblewski
  - Ann Farrell
  - Hylton Joffe
- Project Management
  - Caden Brennen
- Efficacy Statistics
  - Sarabdeep Singh
  - Yeh-Fong Chen
- Safety Statistics
  - (Thanh) Van Tran
  - Hye Soo Cho
  - Clara Kim
  - Mat Soukup
- Clinical Pharmacology
  - Snehal Samant
  - Katarzyna Drozda
  - Sudharshan Hariharan
- Pharmacometrics
  - Yuzhuo Pan
  - Liang Li
- Pharmacology/Toxicology
  - Bo Lee
  - Natalie Simpson
  - Pedro DelValle
- Quality
  - Theodore Carver
  - Sharmista Chatterjee
- Labeling
  - Virginia Kwitkowski
- Clinical Data Science
  - Megan Peach
  - Qunshu Zhang
- Division of Hepatology and Nutrition
  - Paul H. Hayashi
  - Ling Lan
- Office of Scientific Investigations
  - Anthony Orencia
- Division of Clinical Outcome Assessment
  - Yasmin Choudhry
  - Selena Daniels
- Patient-Focused Statistical Support
  - Xin Yuan
  - Lili Garrard

Outline of Presentation

- Product and proposed indication
- Background
- Daprodustat development program
- Efficacy
- Safety
  - All-Cause Mortality
  - Cardiovascular (CV) Safety
  - Gastric Erosions and Acute Kidney Injury (AKI)
- Summary

Product and Proposed Indication

- Daprodustat: small-molecule, hypoxia inducible factor prolyl-hydroxylase inhibitor (HIF-PHI)
- Proposed Indication: For the treatment of anemia due to chronic kidney disease (CKD) in adults not on dialysis and on dialysis
- Orally administered
- Dose adjusted on basis of hemoglobin response

Marketing Status

- Not approved in the United States
- Approved in Japan in June 2020

Anemia in Patients with Chronic Kidney Disease

- Etiology of anemia multifactorial:
  - Erythropoietin deficiency
  - Impaired ability to absorb iron and inability to utilize stored iron
  - Blood loss
  - Shortened red blood cell (RBC) survival
- Current Standard of Care:
  - Iron supplementation (oral or intravenous)
  - Erythropoiesis stimulating agents (ESAs)
  - RBC transfusion

Erythropoiesis Stimulating Agents

- Erythropoiesis stimulating glycoproteins produced by recombinant DNA technology
  - Epoetin alfa (Epogen/Procrit), 1989
  - Darbepoetin alfa (Aranesp), 2001
  - Methoxy polyethylene glycol-epoetin beta (Mircera), 2007
  - Epoetin alfa-epbx (Retacrit), biosimilar to epoetin alfa, 2018
- Approved for the treatment of anemia due to CKD in patients on dialysis and not on dialysis
- Administered intravenously or subcutaneously

Hemoglobin "Target" Studies Have Shaped ESA Labeling

- Four large, randomized, controlled trials:
  - Normal hematocrit study
  - Correction of hemoglobin outcomes in renal insufficiency (CHOIR)
  - Cardiovascular risk reduction by early anemia treatment with epoetin-beta (CREATE) study
  - Trial to reduce cardiovascular events with Aranesp therapy (TREAT)
- All showed (or tended to show) adverse cardiovascular outcomes with higher rather than lower hemoglobin targets
- The optimum hemoglobin target remains unknown

ESA Boxed Warning

- **WARNING: ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access….**
- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin > 11 g/dL.**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest dose sufficient to reduce the need for RBC transfusions.**

ESA Warnings and Precautions

- Increased mortality, myocardial infarction, stroke, and thromboembolism: Using ESAs to target a hemoglobin level >11g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit.
- Hypertension: Control hypertension prior to initiating and during treatment.
- Seizures: ESAs increase the risk of seizures.

Advisory Committee Meeting Following TREAT

- October 2010 – Cardiovascular and Renal Drugs Advisory Committee Meeting

- Question #1 - …should the indication for darbepoetin alfa for … patients not on dialysis be withdrawn?
  - Yes: 1
  - No: 15
  - Abstain: 1

Daprodustat Development Program

- Concurrent Development programs for Anemia of CKD
  - Patients not on dialysis (ND)
  - Patients on dialysis (D)
- Co-Primary Efficacy Endpoint: Change from baseline in Hemoglobin (Hb)
- Co-Primary Safety Endpoint: Major adverse cardiovascular events (MACE)
- General safety assessment: adverse events, laboratory events, vital signs

ASCEND Clinical Program: Design Overview

- ★ ASCEND-ND n=4500
- ★ ASCEND-D n=3000

} Event-driven CVOT

★ **Stand-alone MACE/safety assessment**

CVOT – Cardiovascular Outcomes Trial

ASCEND Clinical Program: Design Overview

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- ASCEND-NHQ n=600
- ASCEND-TD n=402
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} Fixed sample size randomized controlled trials

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● **Placebo Controlled** ▲ **Double blind** ★ **Stand-alone MACE/safety assessment**

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Placebo Controlled **Double blind** **Specific Clinical Scenario** **Stand-alone MACE/safety assessment**

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Placebo Controlled **Double blind** **Specific Clinical Scenario** **Stand-alone MACE/safety assessment**

CVOT – Cardiovascular Outcomes Trial

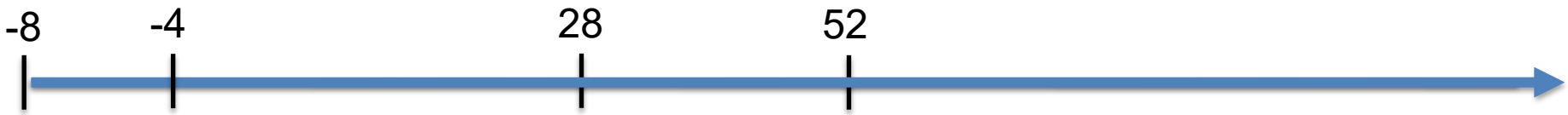
ASCEND-D/ND Trial Design

Inclusion criteria: **ASCEND-D: Stable hemodialysis or peritoneal dialysis + ESA**
ASCEND-ND: Stage 3, 4, or 5 chronic kidney disease +/- ESA

ASCEND-D/ND Trial Design

Inclusion criteria:	**ASCEND-D: Stable hemodialysis or peritoneal dialysis + ESA** **ASCEND-ND: Stage 3, 4, or 5 chronic kidney disease +/- ESA**	*** NYHA Class IV**
Exclusion criteria:	**History of Severe* Heart Failure, Acute Coronary Syndrome, Stroke/Transient Ischemic Attack, Gastrointestinal Bleed, Malignancy**	

Screen



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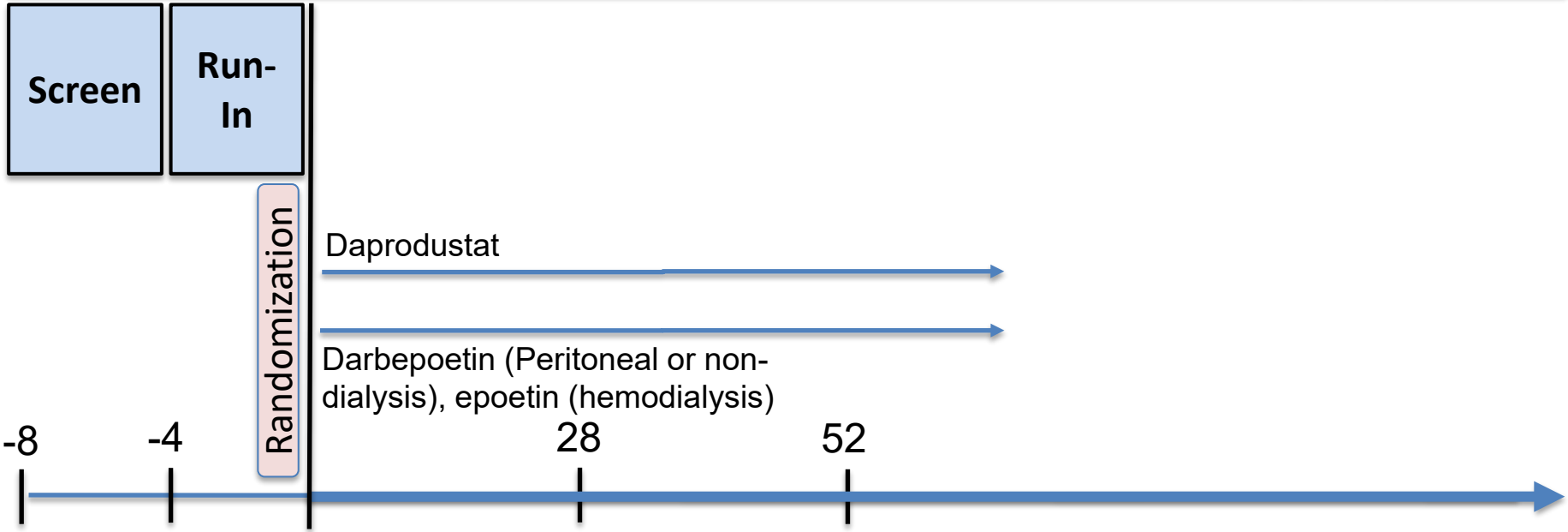

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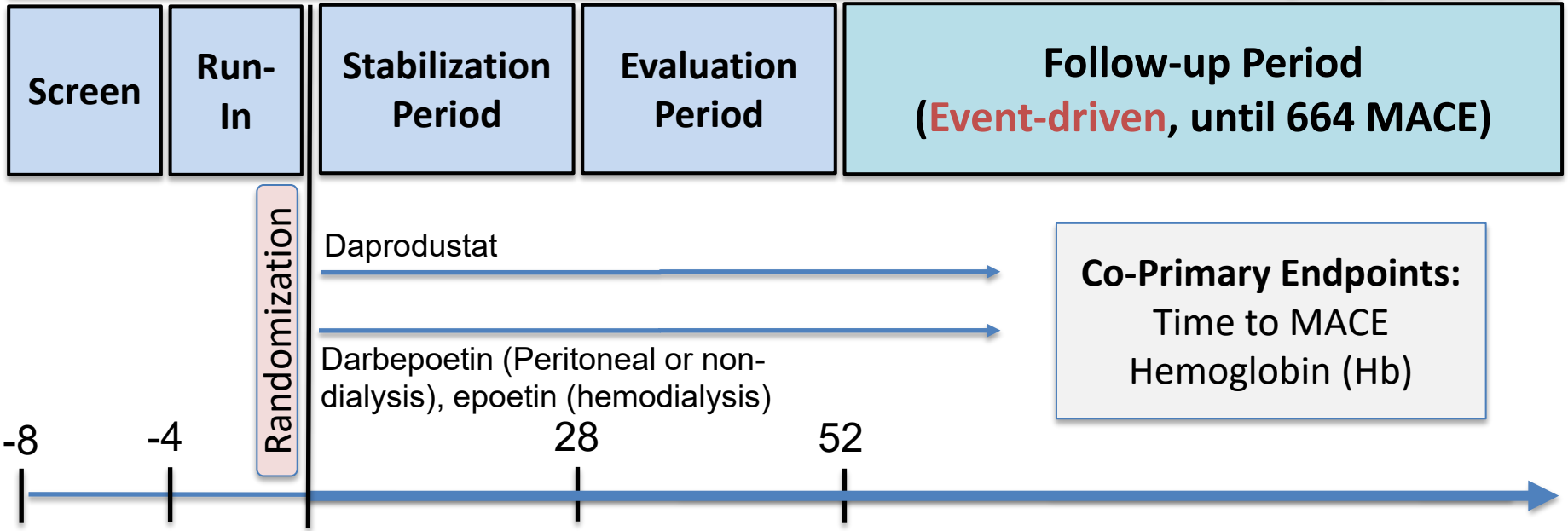

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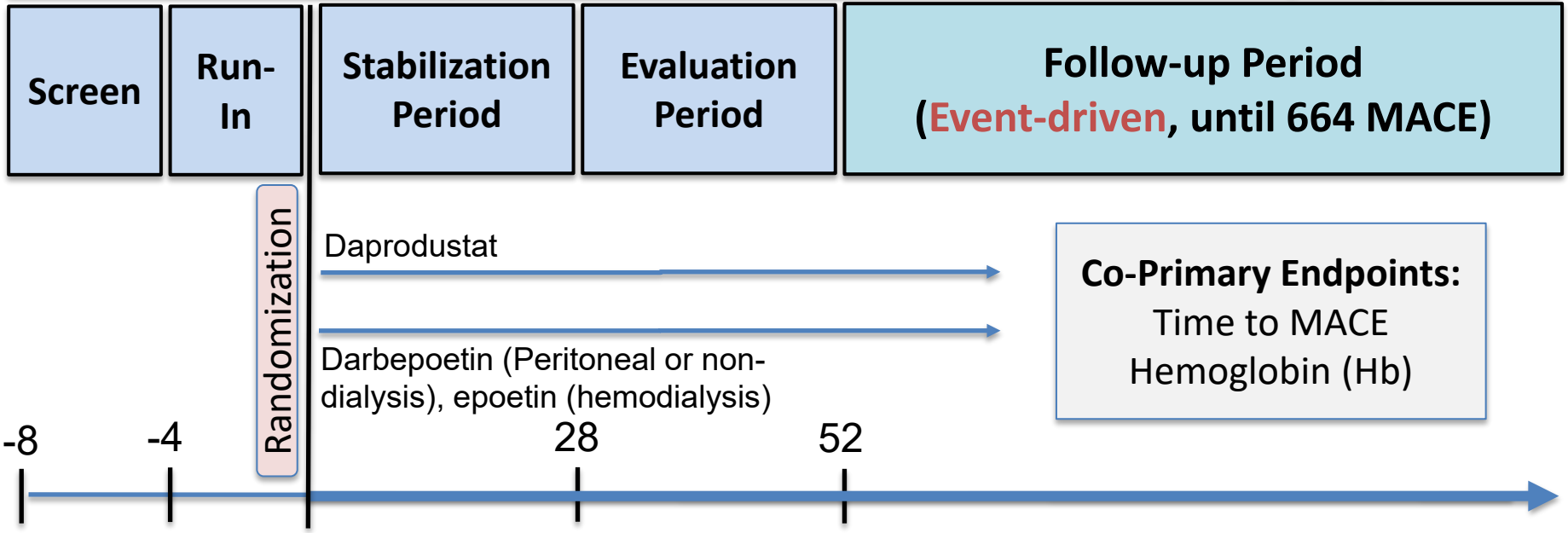

Maintain Iron Repletion; Maintain Hb between 10 - 11 g/dL; Transfuse/Rescue per protocol

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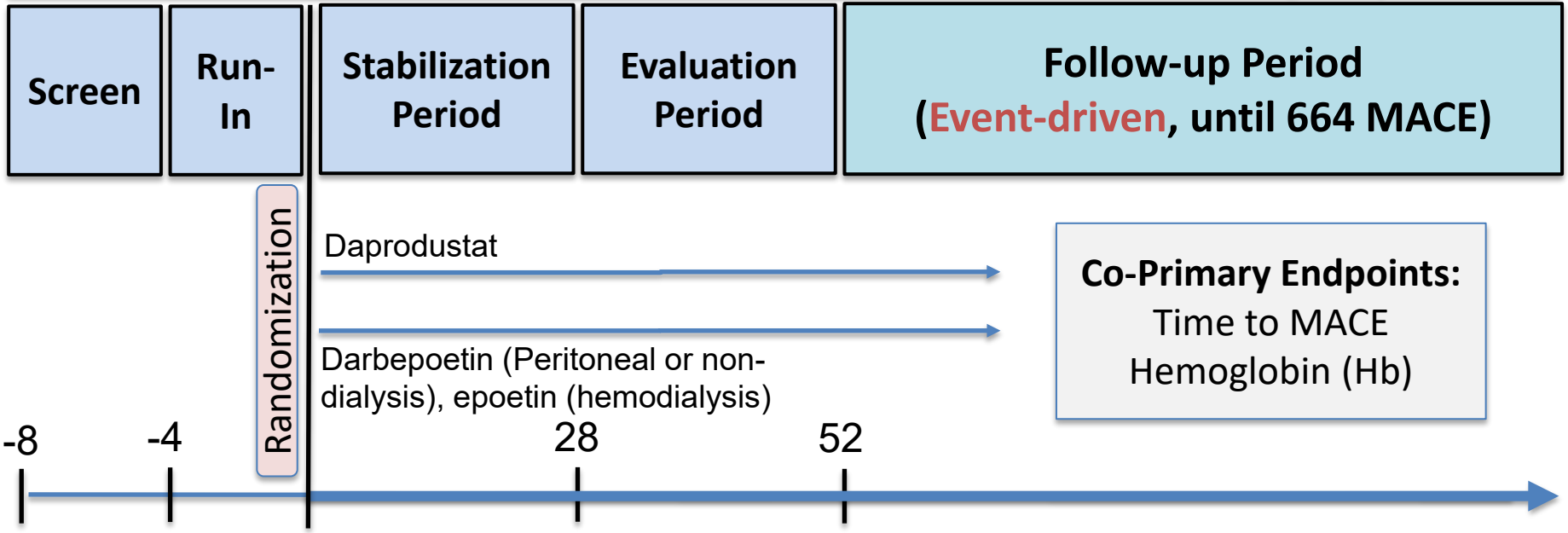

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DEMOGRAPHICS, DISPOSITION AND EXPOSURE

Baseline Demographics

	ASCEND-ND		ASCEND-D	
	Dapro	Darbe	Dapro	ESA
Age, Years (median [IQR])	67 [57, 75]	67 [57, 74]	58 [48, 67]	59 [47, 68]
Male (%)	43	45	57	57
Race (%)				
Asian	27	28	12	12
Black	9	10	15	16
White	57	54	67	67
Other	7	8	6	5
U.S. (%)	25	25	29	29
ESA use (%)	47	47	100	100
Peritoneal dialysis (%)	-	-	12	11

IQR: Interquartile Range

Baseline Demographics

	ASCEND-ND		ASCEND-D	
	Dapro	Darbe	Dapro	ESA
Median eGFR	17	18	-	-
Diabetes (%)	56	59	41	42
Cardiovascular disease (%)	37	37	45	45
Aspirin (%)	30	30	35	36
Vit. K antagonist (%)	4	3	5	5
Clopidogrel (%)	9	9	9	11
Heart failure (%)	18	18	27	26
Median TSAT percent	30	29	33	32
IV iron use (%)	8	9	60	60

eGFR units: mL/min/1.73 m^2
TSAT: Transferrin saturation

Disposition ASCEND-D and ASCEND-ND

Similar rates of study completion between groups

	Study Completion[1]	CRT[2]	Complete CV[3]
ASCEND-D	92%	74%	89%
ASCEND-ND	97%	81%	95%

[1]**Study Completion:** Completed 52 weeks of treatment and through the End-of-Study visit, including subjects who died
[2]**CRT**: Completed 52 weeks of Randomized Treatment and had hemoglobin data observed at Week 52
[3]**Complete CV**: Known Cardiovascular Endpoint Status at End-of-Study, including subjects who died

Disposition ASCEND-D and ASCEND-ND

Similar rates of reasons for treatment discontinuation# between groups

		Daprodustat (%)	ESA (%)
ASCEND-D	**Overall**	**53**	**53**
	Adverse event (incl. death)	16	16
	Withdrawal criterion met	16	15
	Withdrawal by subject	17	19
ASCEND-ND	**Overall**	**38**	**38**
	Adverse event (incl. death)	13	12
	Withdrawal criterion met	8	8
	Withdrawal by subject	15	15

 # Discontinuation: Includes deaths

Drug Exposure of ASCEND-D/ND

		Daprodustat	ESA Comparator
ASCEND-D	# Patients	1487	1477
	Months of Exposure*	26 [11 – 31]	26 [12 – 31]
	Months of Follow Up*	30 [27 – 35]	30 [26 – 35]
	Total Exposure/Follow-Up#	2712/3512 [77]	2745/3483 [79]
ASCEND-ND	# Patients	1937	1935
	Months of Exposure*	18 [7 – 28]	18 [8 – 29]
	Months of Follow Up*	22 [12 – 32]	22 [12 – 32]
	Total Exposure/Follow-Up#	2982/3593 [83]	3056/3592 [85]

* Median [interquartile range]

\# Patient-years [% Exposure/Follow-Up]

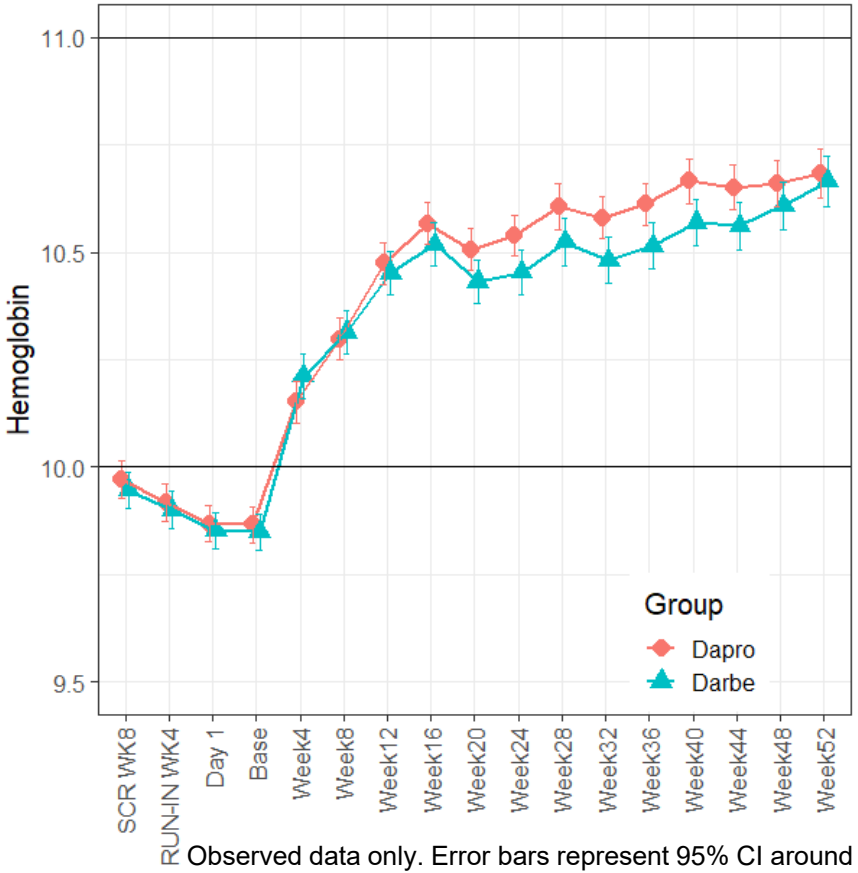
EFFICACY

Major Efficacy Endpoint and Analysis

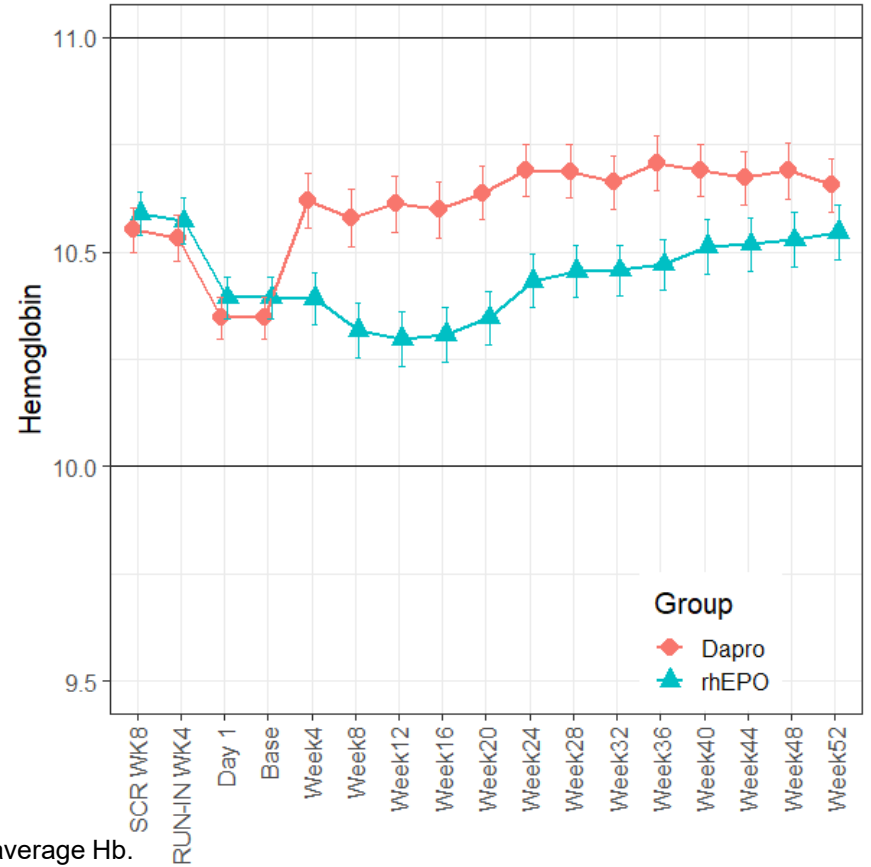
- Co-Primary Endpoint: Mean change in Hb from baseline to the evaluation period regardless of rescue therapy
- Analysis: Test the difference in mean Hb using a noninferiority margin of -0.75 and analysis of covariance (ANCOVA) with multiple imputation
- FDA confirmed the Applicant's efficacy results with respect to hemoglobin and agree that substantial evidence of effectiveness is established

Co-Primary Endpoint: Change in Hb

ASCEND-ND



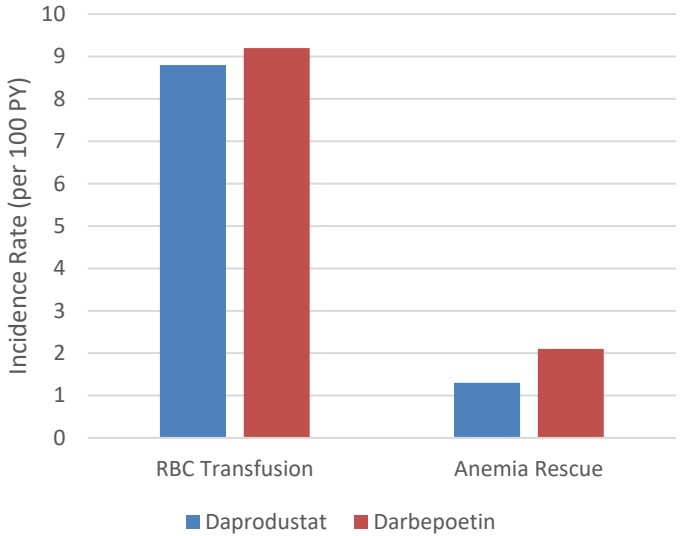
ASCEND-D



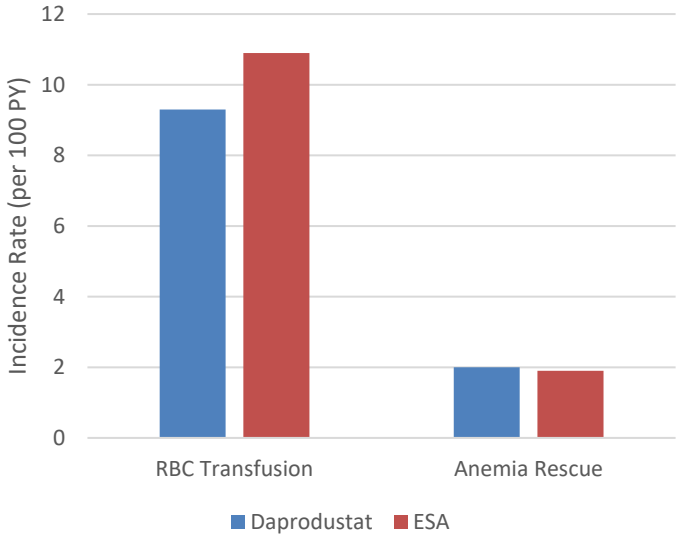
Observed data only. Error bars represent 95% CI around the average Hb.

Incidence Rates of First RBC Transfusion and Anemia Rescue

ASCEND-ND



ASCEND-D



ASCEND-NHQ: Patient-Reported Outcome (PRO)

- ASCEND-NHQ is a 28-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter phase 3 study in non-dialysis patients with anemia associated with CKD

- Key secondary efficacy PRO endpoint was mean change in the 36-item Short Form Health Survey version 2.0 (SF-36 v2.0) Vitality domain between baseline and Week 28

Interpretability of PRO Results

- Daprodustat had statistically significant improvement in the SF-36 v.2.0 Vitality domain score compared with placebo.

- However, the magnitude of the changes at the item- and domain-level (using raw and transformed score scales) were minimal.

- The changes in the SF-36 v.2.0 Vitality domain scores are not considered meaningful improvements from the patient perspective.

Efficacy Summary

- Daprodustat is non-inferior to ESAs in raising Hb
- Similar rates of RBC transfusions
- No other meaningful benefits demonstrated

Daprodustat's Cardiovascular Safety

Cardiovascular and Renal Drugs Advisory Committee Meeting
October 26, 2022

Van Tran, PhD
Mathematical Statistician
Division of Biometrics VII (DB-VII), Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER, FDA

MACE: ASCEND-D and ASCEND-ND

- ASCEND-ND/ASCEND-D objective: Demonstrate non-inferiority of MACE comparing daprodustat to active control
  - Rule out risk margin of 1.25 with upper 95% confidence interval (CI) bound
- MACE: Co-primary endpoint
  - Time to first occurrence of MACE, a composite of:
    - All-cause mortality
    - Non-fatal myocardial infarction (MI)
    - Non-fatal stroke

Other Endpoints – ASCEND-D and ASCEND-ND

- Secondary, pre-specified time to first event endpoints
  - All-cause mortality
  - Cardiovascular (CV) mortality
  - Fatal/non-fatal myocardial infarction
  - Fatal/non-fatal stroke
  - Fatal/non-fatal hospitalization for heart failure (HHF)
  - Fatal/non-fatal thromboembolic event (TEE)
- Exploratory time to first event endpoints
  - CV MACE (composite of CV mortality, nonfatal MI, nonfatal stroke)
  - Vascular access thrombosis (a type of TEE)
- MACE and CV endpoints were adjudicated by an external independent Clinical Events Committee

Statistical Analyses

- Primary analysis population: Intention-to-Treat population, defined as all randomized subjects analyzed according to the treatment to which subjects were randomized
- Event ascertainment windows
  - On-study (primary)
  - On-treatment (supportive)
- Primary analysis: Cox proportional hazards model adjusted for baseline variables used in stratified randomization[1]
- Analyses of secondary/exploratory CV endpoints and subgroups were not multiplicity controlled

[1] Covariates: region (Asia Pacific, Eastern Europe/South Africa, Western Europe/Canada/ANZ, Latin America, U.S.), current ESA use (ASCEND-ND only: User, Non-user), dialysis type (ASCEND-D only: HD, PD)

FDA Focus: On-Study Analysis

- Focus should be on On-study analysis estimates
  - Design and conduct of ASCEND-ND and ASCEND-D suitable for On-study analysis
  - Preserves integrity of randomization
- On-treatment analysis results were inconsistent with On-study results for MACE
  - On-treatment analysis is subject to bias

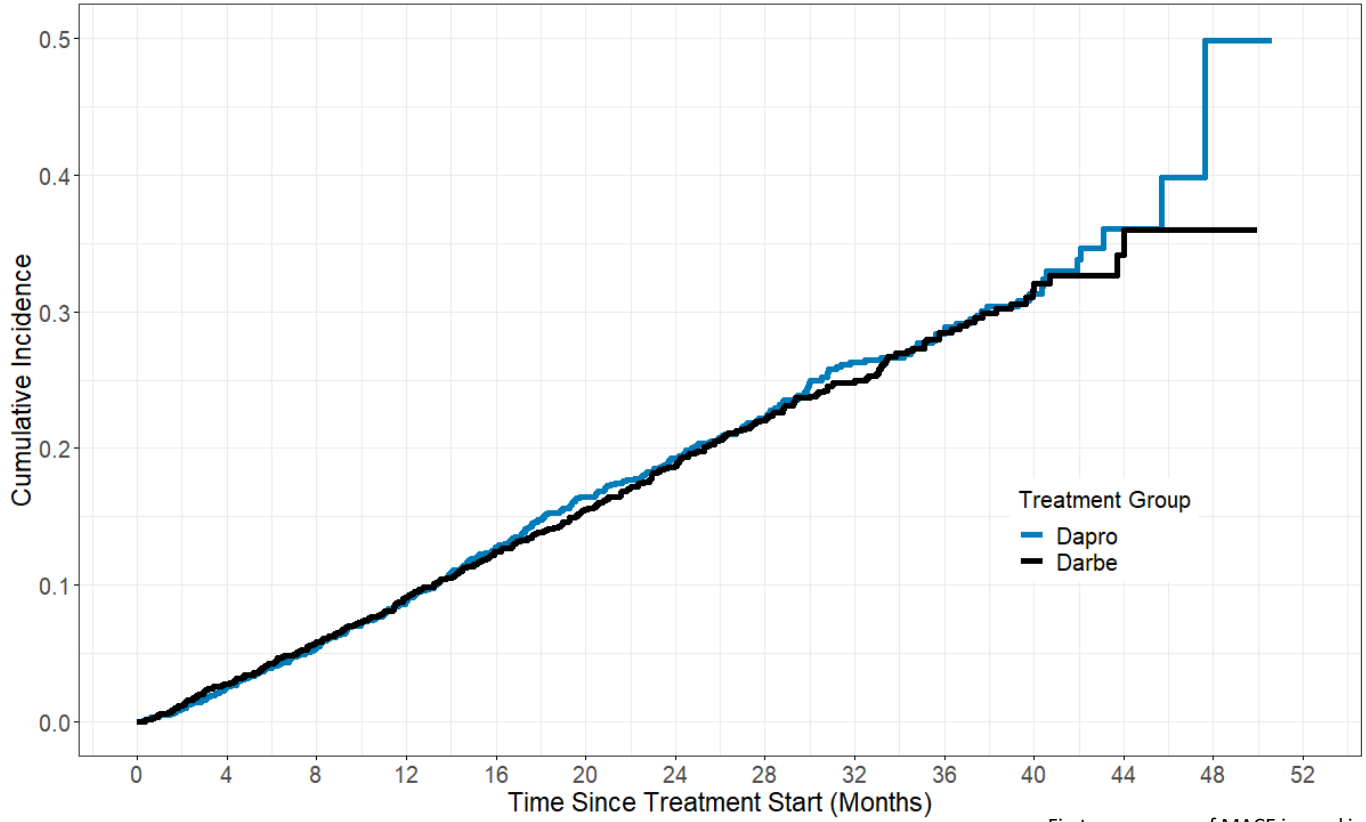
ANALYSIS RESULTS - ASCEND-ND

MACE Primary Analysis (On-Study) – ASCEND-ND

	Daprodustat N=1937 PY=3480	Darbepoetin N=1935 PY=3489	Hazard Ratio (95% CI)
MACE, n [IR]	378 [10.9]	371 [10.6]	1.03 (0.89, 1.19)
All-cause mortality, n[1] (%)	252 (67)	259 (70)	-
Non-fatal myocardial infarction, n[1] (%)	96 (25)	91 (25)	-
Non-fatal stroke, n[1] (%)	30 (8)	21 (6)	-

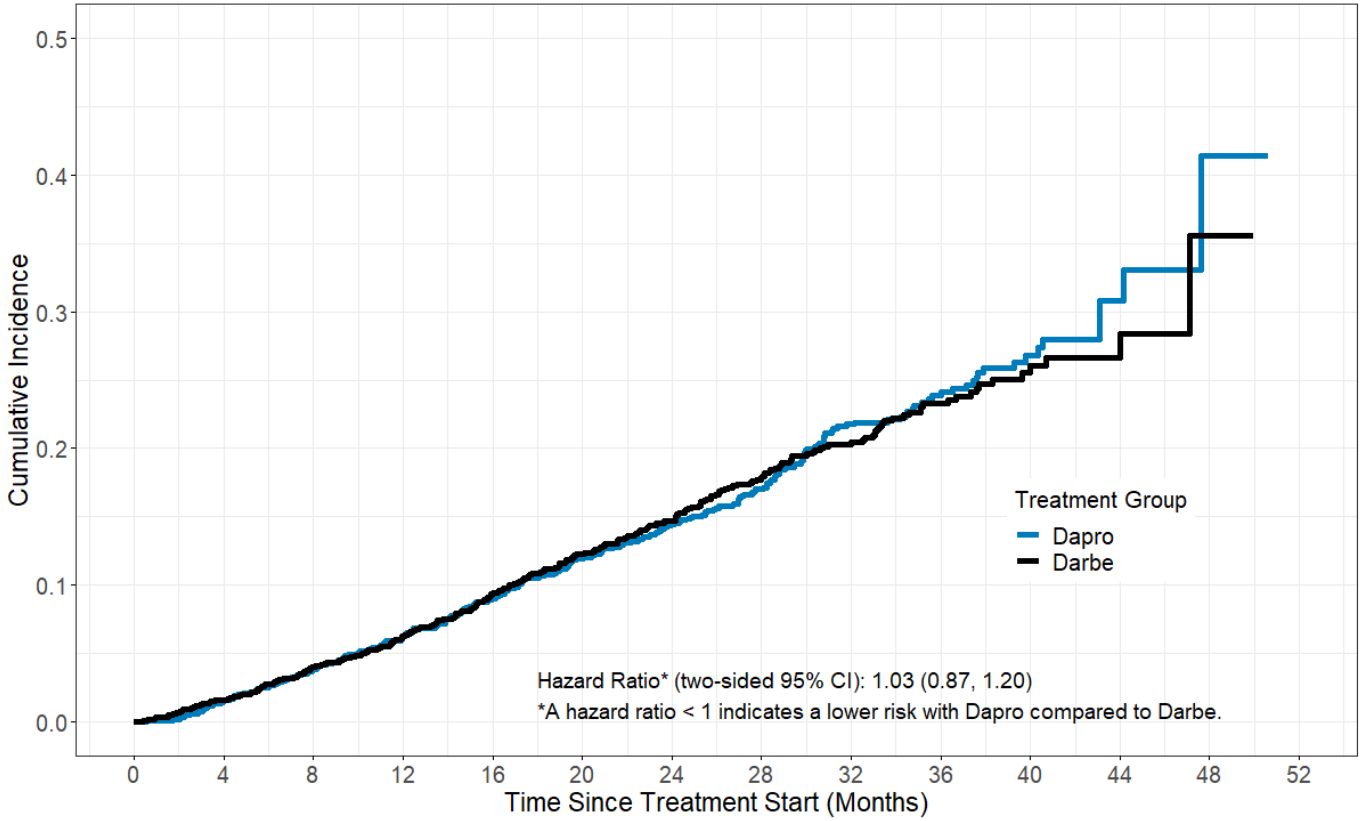
IR: incidence rate per 100 PY; PY: person-year; %: percentage of MACE
First occurrence of MACE is used in the analyses
[1] A subject was counted only once (first component event) in the component summary of MACE

MACE Kaplan-Meier Curves – ASCEND-ND

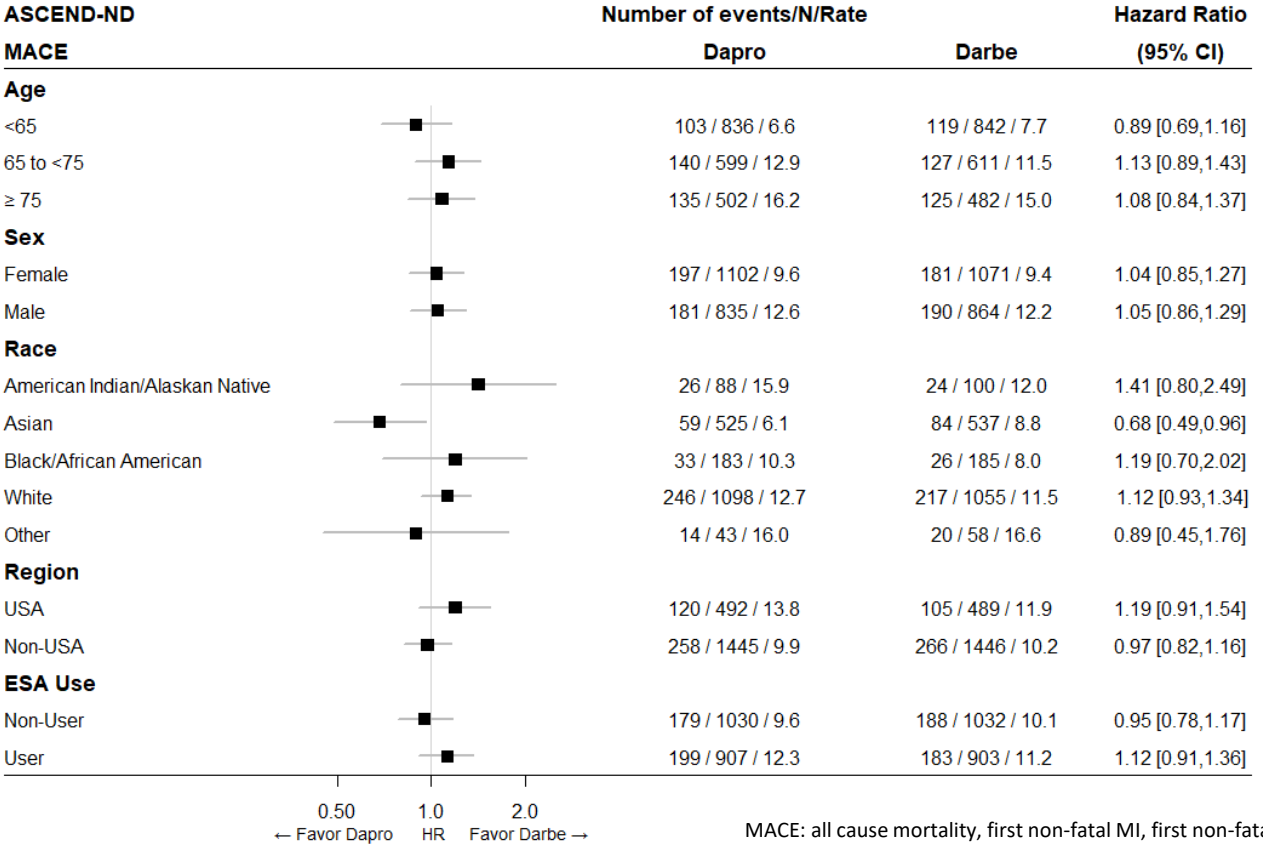


First occurrence of MACE is used in the analysis
Dapro: daprodustat
Darbe: darbepoetin

All-Cause Mortality Kaplan-Meier Curves– ASCEND-ND



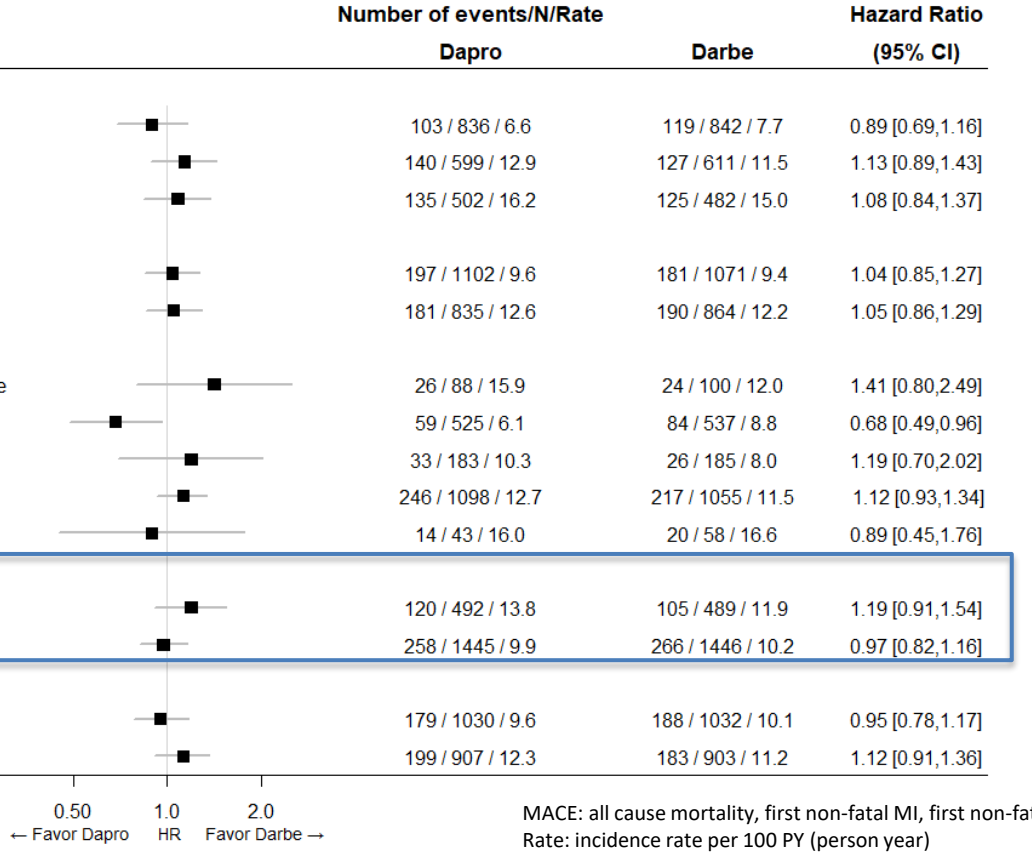
MACE Subgroup Analyses (On-Study) – ASCEND-ND



ASCEND-ND MACE	Number of events/N/Rate Dapro	Darbe	Hazard Ratio (95% CI)
Age			
<65	103 / 836 / 6.6	119 / 842 / 7.7	0.89 [0.69,1.16]
65 to <75	140 / 599 / 12.9	127 / 611 / 11.5	1.13 [0.89,1.43]
≥ 75	135 / 502 / 16.2	125 / 482 / 15.0	1.08 [0.84,1.37]
Sex			
Female	197 / 1102 / 9.6	181 / 1071 / 9.4	1.04 [0.85,1.27]
Male	181 / 835 / 12.6	190 / 864 / 12.2	1.05 [0.86,1.29]
Race			
American Indian/Alaskan Native	26 / 88 / 15.9	24 / 100 / 12.0	1.41 [0.80,2.49]
Asian	59 / 525 / 6.1	84 / 537 / 8.8	0.68 [0.49,0.96]
Black/African American	33 / 183 / 10.3	26 / 185 / 8.0	1.19 [0.70,2.02]
White	246 / 1098 / 12.7	217 / 1055 / 11.5	1.12 [0.93,1.34]
Other	14 / 43 / 16.0	20 / 58 / 16.6	0.89 [0.45,1.76]
Region			
USA	120 / 492 / 13.8	105 / 489 / 11.9	1.19 [0.91,1.54]
Non-USA	258 / 1445 / 9.9	266 / 1446 / 10.2	0.97 [0.82,1.16]
ESA Use			
Non-User	179 / 1030 / 9.6	188 / 1032 / 10.1	0.95 [0.78,1.17]
User	199 / 907 / 12.3	183 / 903 / 11.2	1.12 [0.91,1.36]

MACE: all cause mortality, first non-fatal MI, first non-fatal stroke
Rate: incidence rate per 100 PY (person year)

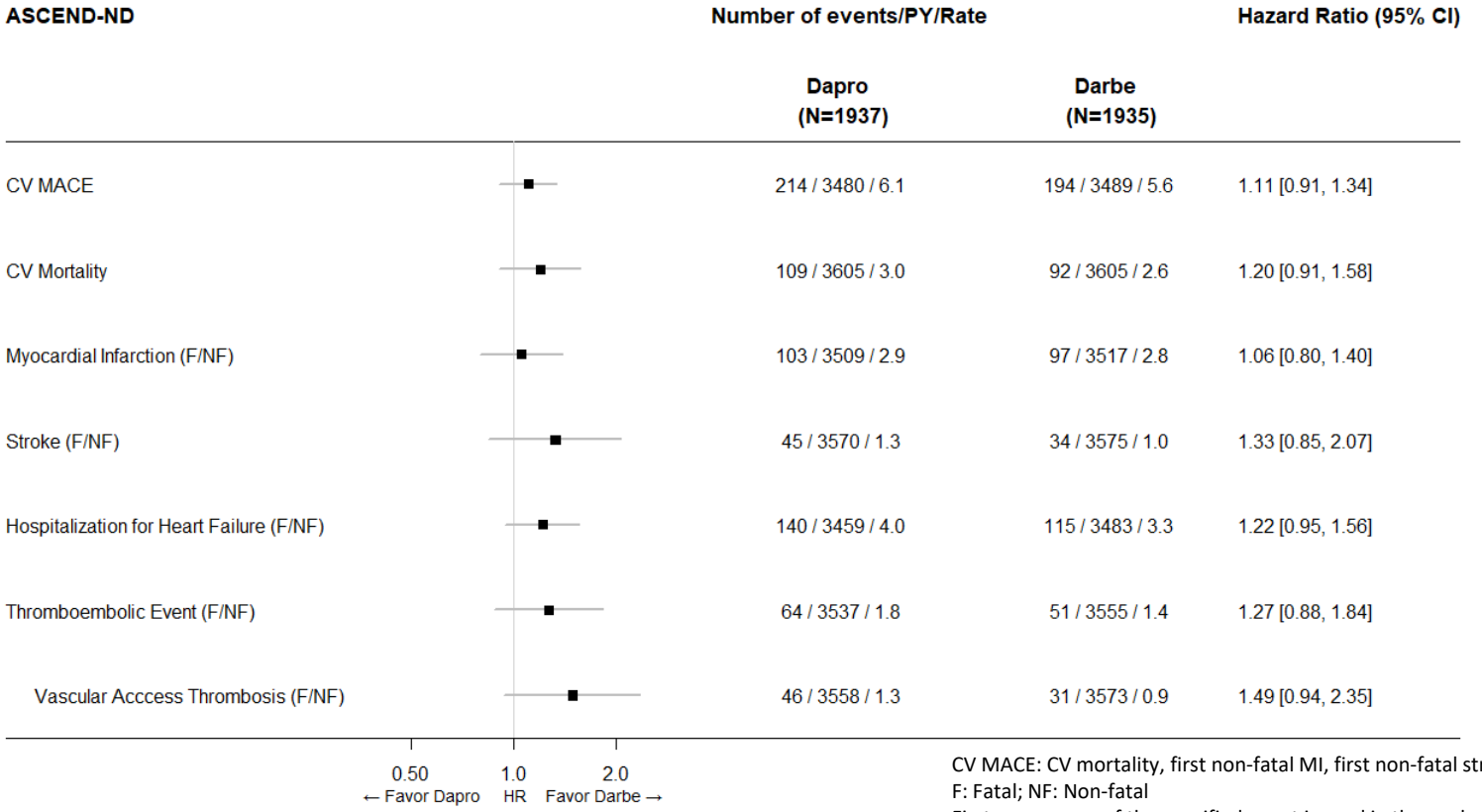
MACE Subgroup Analyses (On-Study) – ASCEND-ND



ASCEND-ND MACE	Number of events/N/Rate Dapro	Darbe	Hazard Ratio (95% CI)
Age			
<65	103 / 836 / 6.6	119 / 842 / 7.7	0.89 [0.69,1.16]
65 to <75	140 / 599 / 12.9	127 / 611 / 11.5	1.13 [0.89,1.43]
≥ 75	135 / 502 / 16.2	125 / 482 / 15.0	1.08 [0.84,1.37]
Sex			
Female	197 / 1102 / 9.6	181 / 1071 / 9.4	1.04 [0.85,1.27]
Male	181 / 835 / 12.6	190 / 864 / 12.2	1.05 [0.86,1.29]
Race			
American Indian/Alaskan Native	26 / 88 / 15.9	24 / 100 / 12.0	1.41 [0.80,2.49]
Asian	59 / 525 / 6.1	84 / 537 / 8.8	0.68 [0.49,0.96]
Black/African American	33 / 183 / 10.3	26 / 185 / 8.0	1.19 [0.70,2.02]
White	246 / 1098 / 12.7	217 / 1055 / 11.5	1.12 [0.93,1.34]
Other	14 / 43 / 16.0	20 / 58 / 16.6	0.89 [0.45,1.76]
Region			
USA	120 / 492 / 13.8	105 / 489 / 11.9	1.19 [0.91,1.54]
Non-USA	258 / 1445 / 9.9	266 / 1446 / 10.2	0.97 [0.82,1.16]
ESA Use			
Non-User	179 / 1030 / 9.6	188 / 1032 / 10.1	0.95 [0.78,1.17]
User	199 / 907 / 12.3	183 / 903 / 11.2	1.12 [0.91,1.36]

MACE: all cause mortality, first non-fatal MI, first non-fatal stroke
Rate: incidence rate per 100 PY (person year)

CV Endpoints Analysis (On-Study) – ASCEND-ND

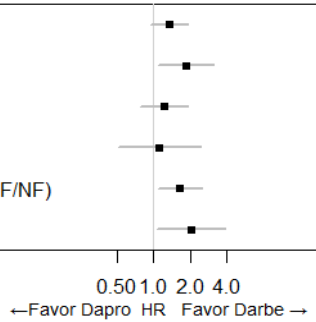


ASCEND-ND	Number of events/PY/Rate		Hazard Ratio (95% CI)
	Dapro (N=1937)	Darbe (N=1935)	
CV MACE	214 / 3480 / 6.1	194 / 3489 / 5.6	1.11 [0.91, 1.34]
CV Mortality	109 / 3605 / 3.0	92 / 3605 / 2.6	1.20 [0.91, 1.58]
Myocardial Infarction (F/NF)	103 / 3509 / 2.9	97 / 3517 / 2.8	1.06 [0.80, 1.40]
Stroke (F/NF)	45 / 3570 / 1.3	34 / 3575 / 1.0	1.33 [0.85, 2.07]
Hospitalization for Heart Failure (F/NF)	140 / 3459 / 4.0	115 / 3483 / 3.3	1.22 [0.95, 1.56]
Thromboembolic Event (F/NF)	64 / 3537 / 1.8	51 / 3555 / 1.4	1.27 [0.88, 1.84]
Vascular Acccess Thrombosis (F/NF)	46 / 3558 / 1.3	31 / 3573 / 0.9	1.49 [0.94, 2.35]

CV MACE: CV mortality, first non-fatal MI, first non-fatal stroke
F: Fatal; NF: Non-fatal
First occurrence of the specified event is used in the analyses
Rate: incidence rate per 100 PY (person year)

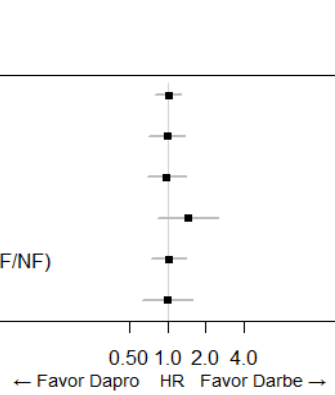
Region Subgroup Analyses (On-Study) – ASCEND-ND

USA



Endpoint	Number of events/N/Rate Dapro	Darbe	Hazard Ratio (95% CI)
CV MACE	74 / 492 / 8.5	56 / 489 / 6.3	1.35 [0.95, 1.90]
CV Mortality	40 / 492 / 4.4	22 / 489 / 2.4	1.86 [1.10, 3.12]
Myocardial Infarction (F/NF)	40 / 492 / 4.6	34 / 489 / 3.8	1.21 [0.77, 1.91]
Stroke (F/NF)	13 / 492 / 1.4	12 / 489 / 1.3	1.11 [0.51, 2.44]
Hospitalization for Heart Failure (F/NF)	58 / 492 / 6.8	36 / 489 / 4.1	1.65 [1.09, 2.50]
Thromboembolic Event (F/NF)	27 / 492 / 3.1	14 / 489 / 1.5	2.03 [1.06, 3.87]

Non-USA



Endpoint	Number of events/N/Rate Dapro	Darbe	Hazard Ratio (95% CI)
CV MACE	140 / 1445 / 5.4	138 / 1446 / 5.3	1.01 [0.80, 1.28]
CV Mortality	69 / 1445 / 2.6	70 / 1446 / 2.6	0.99 [0.71, 1.38]
Myocardial Infarction (F/NF)	63 / 1445 / 2.4	63 / 1446 / 2.4	0.98 [0.69, 1.40]
Stroke (F/NF)	32 / 1445 / 1.2	22 / 1446 / 0.8	1.44 [0.84, 2.48]
Hospitalization for Heart Failure (F/NF)	82 / 1445 / 3.1	79 / 1446 / 3.0	1.02 [0.75, 1.39]
Thromboembolic Event (F/NF)	37 / 1445 / 1.4	37 / 1446 / 1.4	0.99 [0.63, 1.57]

CV MACE: Time to first CV death, non-fatal MI, non-fatal stroke
Rate: incidence rate per 100 PY (person year)

ASCEND-ND Summary

- Analysis of MACE (hazard ratio [HR] 1.03; CI 0.89, 1.19) ruled out risk margin of 1.25
  - Overlapping Kaplan-Meier curves
- All-cause mortality (HR 1.03; CI 0.87, 1.20) similar between daprodustat and control
- HR estimates >1.0 (ranging from 1.06 to 1.49) for adjudicated CV endpoints
  - U.S. subgroup had greater HR estimates for CV endpoints (except stroke) than non-U.S. subgroup
- Limitations of CV endpoint analyses and subgroup analyses
  - HR estimates had lower precision (compared to MACE)
  - No Type I error control

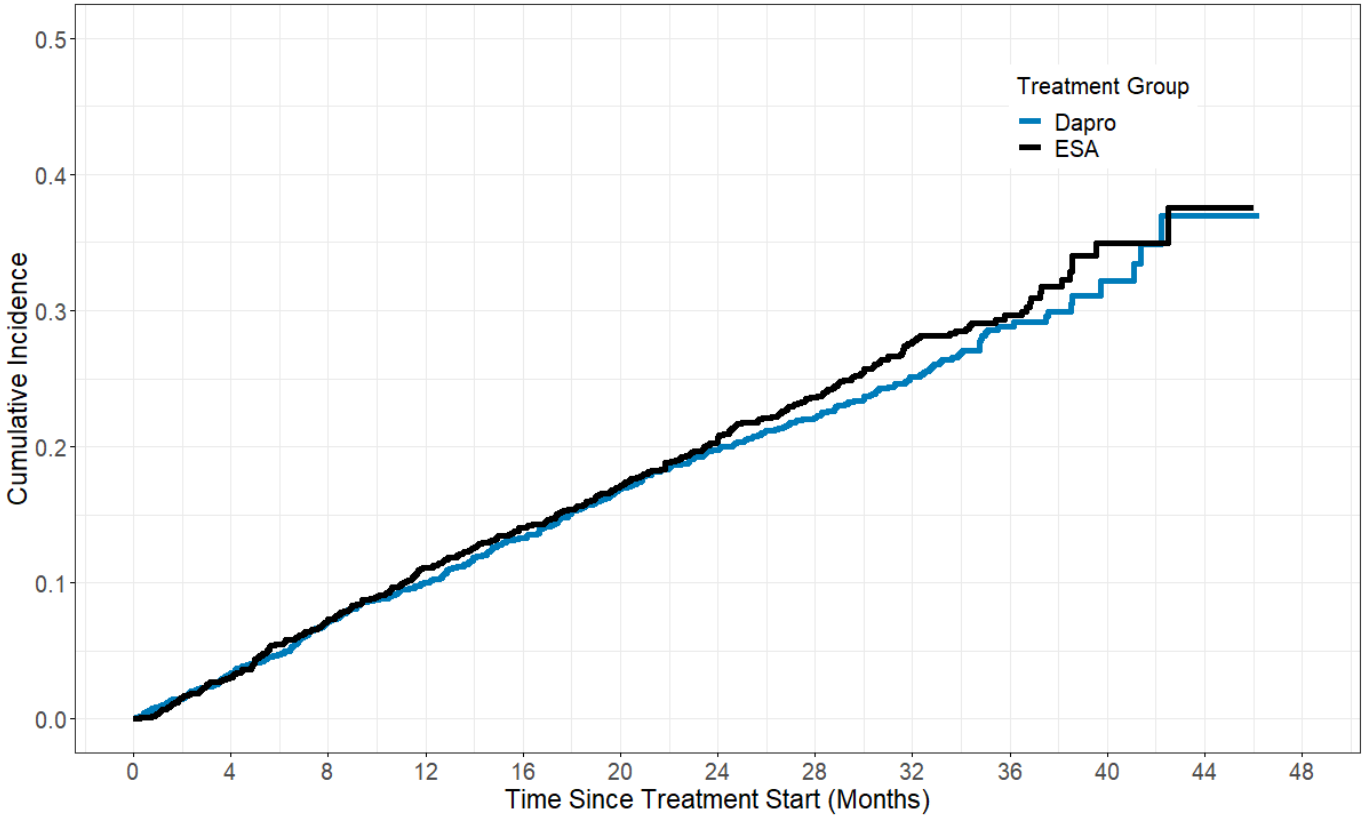
ANALYSIS RESULTS — ASCEND-D

MACE Primary Analysis (On-Study) – ASCEND-D

	Daprodustat N=1487 PY=3377	ESA N=1477 PY=3323	Hazard Ratio (95% CI)
MACE, n [IR]	374 [11.1]	394 [11.9]	0.93 (0.81, 1.07)
All-cause mortality, n[1](%)	244 (65)	233 (59)	-
Non-fatal myocardial infarction, n[1](%)	101 (27)	126 (32)	-
Non-fatal stroke, n[1](%)	29 (8)	35 (9)	-

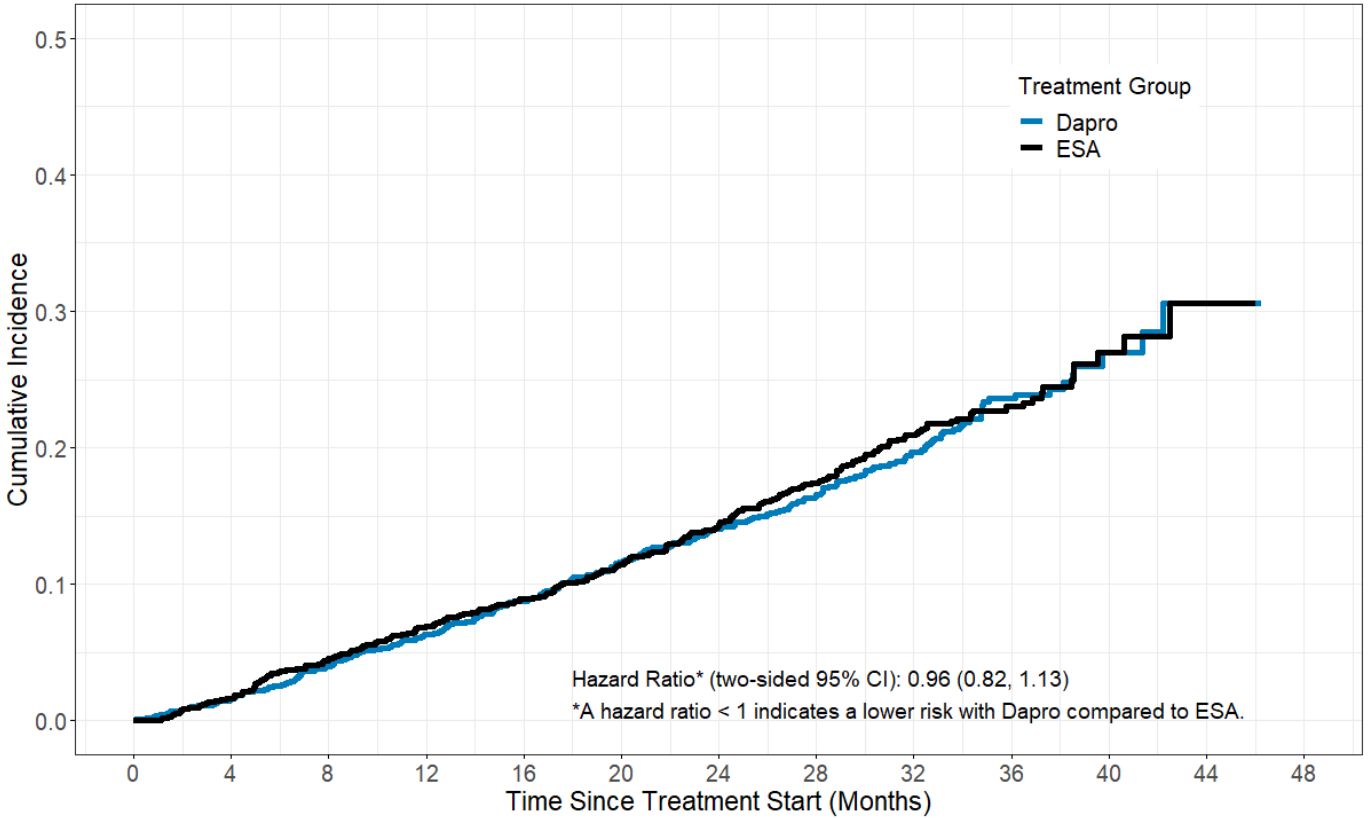
IR: incidence rate per 100 PY; PY: person-year; % Percentage of MACE
First occurrence of MACE is used in the analyses
[1] A subject was counted only once (first component event) in the component summary of MACE

MACE Kaplan-Meier Curves– ASCEND-D

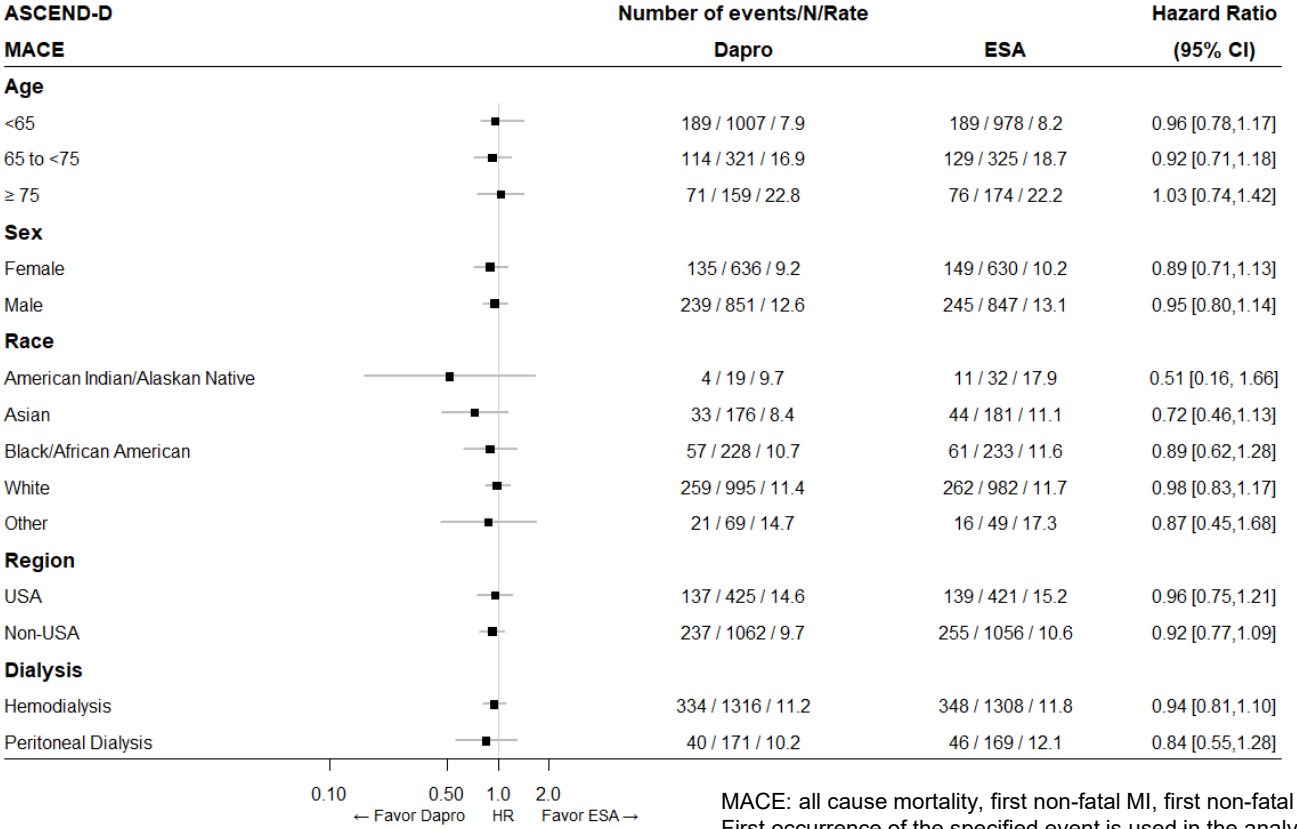


First occurrence of MACE is used in the analysis

All-Cause Mortality Kaplan-Meier Curves– ASCEND-D



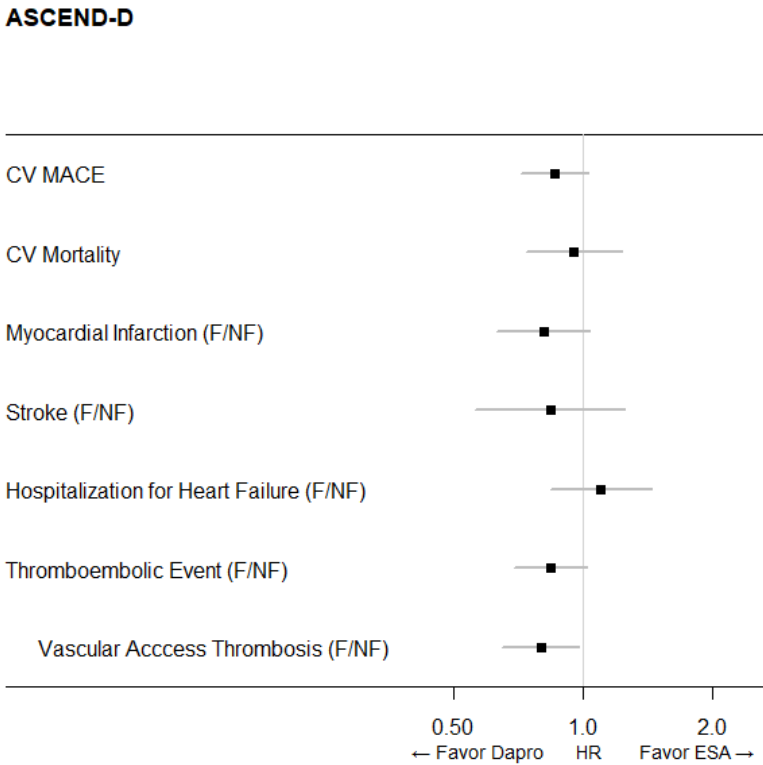
MACE Subgroup Analyses (On-Study) – ASCEND-D



ASCEND-D MACE	Number of events/N/Rate Dapro	ESA	Hazard Ratio (95% CI)
Age			
<65	189 / 1007 / 7.9	189 / 978 / 8.2	0.96 [0.78,1.17]
65 to <75	114 / 321 / 16.9	129 / 325 / 18.7	0.92 [0.71,1.18]
≥ 75	71 / 159 / 22.8	76 / 174 / 22.2	1.03 [0.74,1.42]
Sex			
Female	135 / 636 / 9.2	149 / 630 / 10.2	0.89 [0.71,1.13]
Male	239 / 851 / 12.6	245 / 847 / 13.1	0.95 [0.80,1.14]
Race			
American Indian/Alaskan Native	4 / 19 / 9.7	11 / 32 / 17.9	0.51 [0.16, 1.66]
Asian	33 / 176 / 8.4	44 / 181 / 11.1	0.72 [0.46,1.13]
Black/African American	57 / 228 / 10.7	61 / 233 / 11.6	0.89 [0.62,1.28]
White	259 / 995 / 11.4	262 / 982 / 11.7	0.98 [0.83,1.17]
Other	21 / 69 / 14.7	16 / 49 / 17.3	0.87 [0.45,1.68]
Region			
USA	137 / 425 / 14.6	139 / 421 / 15.2	0.96 [0.75,1.21]
Non-USA	237 / 1062 / 9.7	255 / 1056 / 10.6	0.92 [0.77,1.09]
Dialysis			
Hemodialysis	334 / 1316 / 11.2	348 / 1308 / 11.8	0.94 [0.81,1.10]
Peritoneal Dialysis	40 / 171 / 10.2	46 / 169 / 12.1	0.84 [0.55,1.28]

MACE: all cause mortality, first non-fatal MI, first non-fatal stroke
First occurrence of the specified event is used in the analyses
Rate: incidence rate per 100 PY (person year)

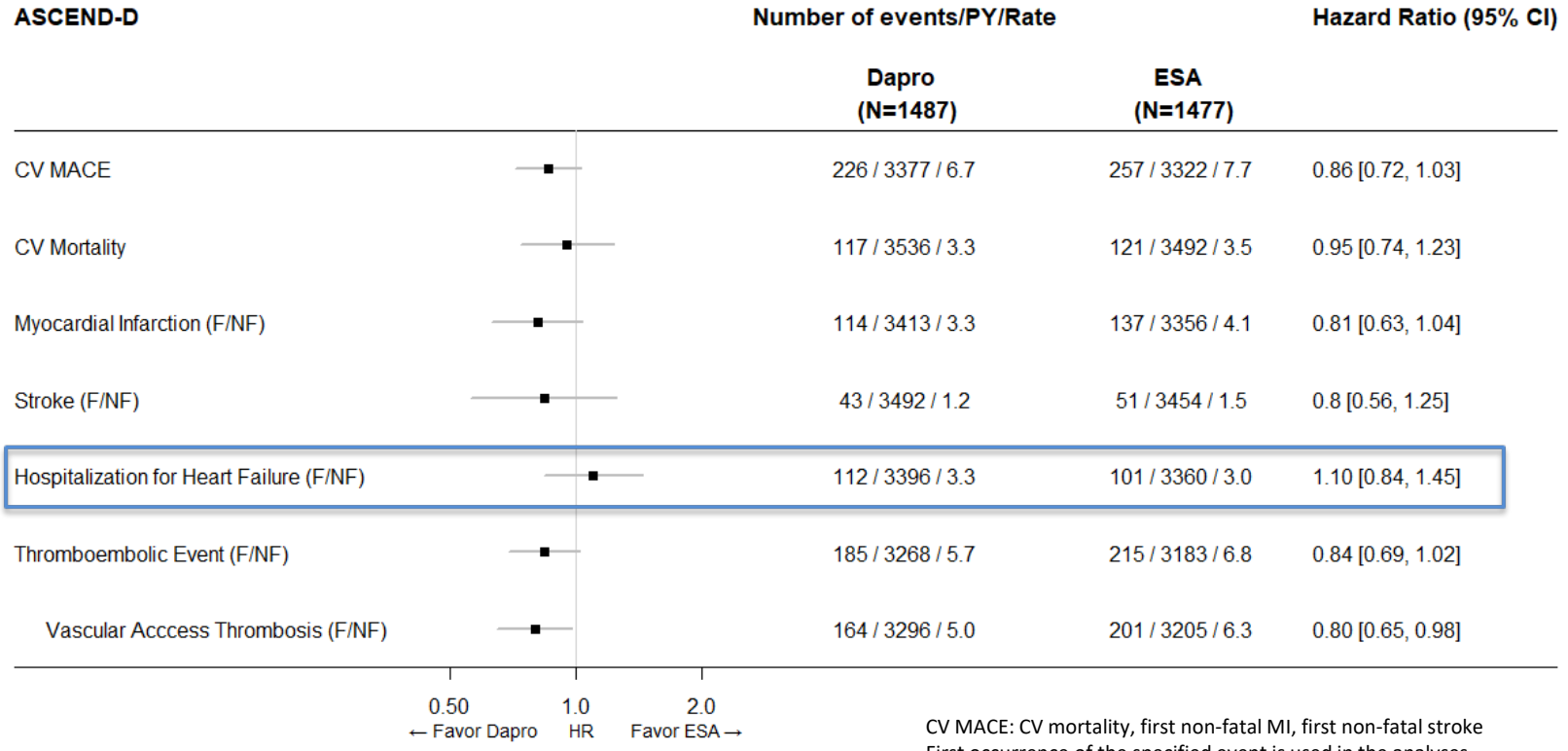
CV Endpoint Analysis (On-Study) – ASCEND-D



ASCEND-D	Number of events/PY/Rate		Hazard Ratio (95% CI)
	Dapro (N=1487)	ESA (N=1477)	
CV MACE	226 / 3377 / 6.7	257 / 3322 / 7.7	0.86 [0.72, 1.03]
CV Mortality	117 / 3536 / 3.3	121 / 3492 / 3.5	0.95 [0.74, 1.23]
Myocardial Infarction (F/NF)	114 / 3413 / 3.3	137 / 3356 / 4.1	0.81 [0.63, 1.04]
Stroke (F/NF)	43 / 3492 / 1.2	51 / 3454 / 1.5	0.8 [0.56, 1.25]
Hospitalization for Heart Failure (F/NF)	112 / 3396 / 3.3	101 / 3360 / 3.0	1.10 [0.84, 1.45]
Thromboembolic Event (F/NF)	185 / 3268 / 5.7	215 / 3183 / 6.8	0.84 [0.69, 1.02]
Vascular Acccess Thrombosis (F/NF)	164 / 3296 / 5.0	201 / 3205 / 6.3	0.80 [0.65, 0.98]

CV MACE: CV mortality, first non-fatal MI, first non-fatal stroke
First occurrence of the specified event is used in the analyses
Rate: incidence rate per 100 PY (person year)

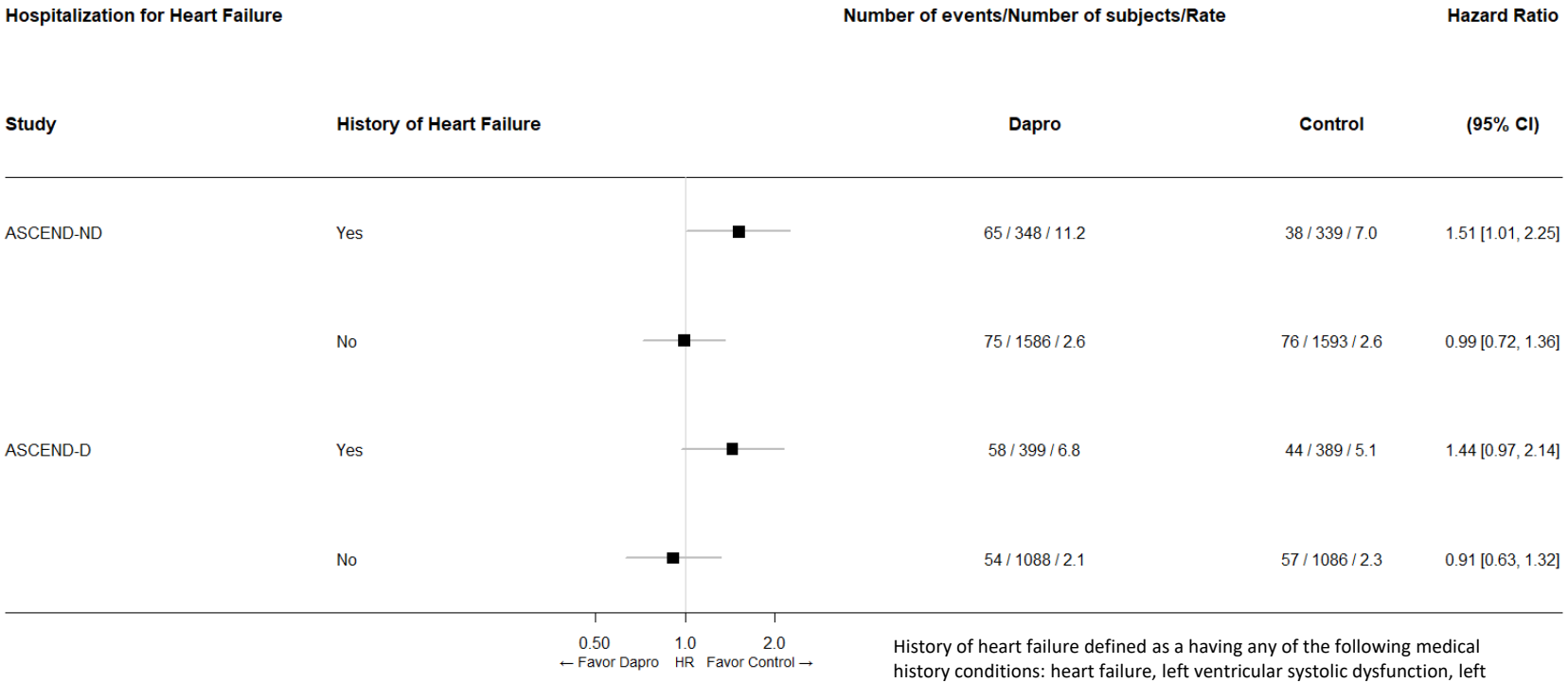
CV Endpoint Analysis (On-Study) – ASCEND-D



ASCEND-D	Number of events/PY/Rate		Hazard Ratio (95% CI)
	Dapro (N=1487)	ESA (N=1477)	
CV MACE	226 / 3377 / 6.7	257 / 3322 / 7.7	0.86 [0.72, 1.03]
CV Mortality	117 / 3536 / 3.3	121 / 3492 / 3.5	0.95 [0.74, 1.23]
Myocardial Infarction (F/NF)	114 / 3413 / 3.3	137 / 3356 / 4.1	0.81 [0.63, 1.04]
Stroke (F/NF)	43 / 3492 / 1.2	51 / 3454 / 1.5	0.8 [0.56, 1.25]
Hospitalization for Heart Failure (F/NF)	112 / 3396 / 3.3	101 / 3360 / 3.0	1.10 [0.84, 1.45]
Thromboembolic Event (F/NF)	185 / 3268 / 5.7	215 / 3183 / 6.8	0.84 [0.69, 1.02]
Vascular Acccess Thrombosis (F/NF)	164 / 3296 / 5.0	201 / 3205 / 6.3	0.80 [0.65, 0.98]

CV MACE: CV mortality, first non-fatal MI, first non-fatal stroke
First occurrence of the specified event is used in the analyses
Rate: incidence rate per 100 PY (person year)

Hospitalization for Heart Failure Subgroup Analysis (On-Study) – ASCEND-D/ASCEND-ND



History of heart failure defined as a having any of the following medical history conditions: heart failure, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, or pulmonary hypertension.
Analyses did not include six subjects (ASCEND-ND) and two subjects (ASCEND-D) missing history of hemofiltration.

ASCEND-D Summary

- Analysis of MACE (HR 0.93; CI 0.81, 1.07) ruled out risk margin of 1.25
  - Overlapping Kaplan-Meier curves
  - Subgroup analysis estimates consistent with overall study population estimate
- All-cause mortality (HR 0.96; CI 0.82, 1.13) was similar between daprodustat and control
- HR estimates >1.0 for HHF (1.22; CI 0.95, 1.56) comparing daprodustat to control
  - Subgroup with history of heart failure had greater HR estimate for HHF than subgroup without history of heart failure
- Other CV endpoints had HR estimates <1.0
- Limitations of CV endpoint analyses and subgroup analyses
  - HR estimates had lower precision (compared to MACE)
  - No Type I error control

Daprodustat's General Safety and Summary

Cardiovascular and Renal Drugs Advisory Committee Meeting
October 26, 2022

Justin Penzenstadler, PharmD
Clinical Reviewer
Office of Cardiology, Hematology and Nephrology (OCHEN)
Center for Drug Evaluation and Research (CDER), FDA

Overview of Other Adverse Events

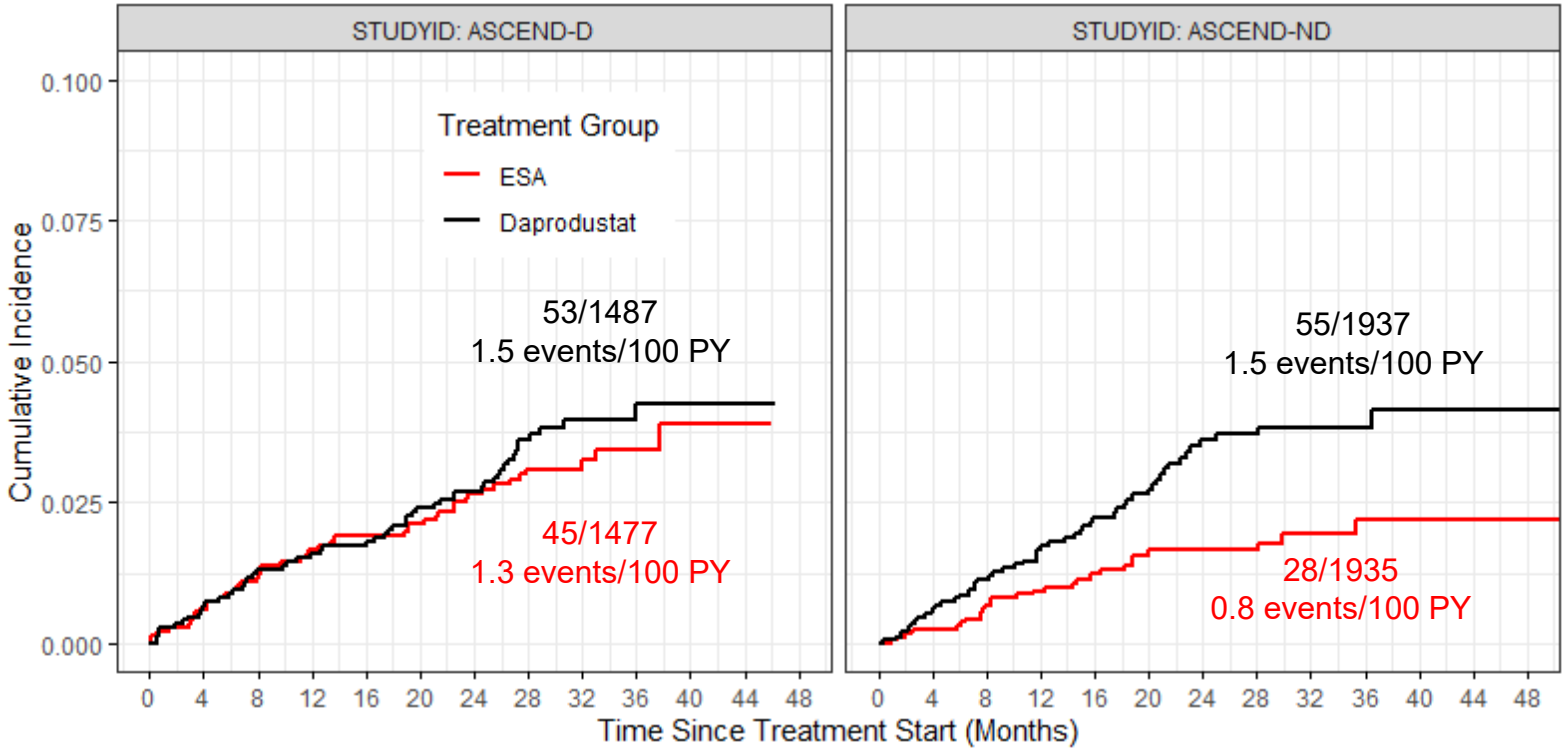
- Notable differences observed in daprodustat vs. ESAs – carries additional risk
  - Gastrointestinal Erosions/Bleeds
  - Acute Kidney Injury (ASCEND-ND only)
- No notable differences observed in daprodustat vs. ESAs – presumably carries the same risk
  - Hypertension
  - Seizures
  - Sepsis
  - Tumor progression/Recurrence

Gastrointestinal Bleeding - ASCEND-ND and ASCEND-D

Treatment difference in serious esophageal and gastric erosions disfavoring daprodustat in both ASCEND-D and ASCEND-ND

- Most events were overt gastrointestinal bleeding, with over one-half requiring transfusion
- Events were ascertained as an AE of special interest, but were not adjudicated
- Treatment arms were balanced for antiplatelets, anticoagulants, and prophylactic agents (e.g., antiacids)

Gastrointestinal Erosions/Bleeding - ASCEND-D and ASCEND-ND



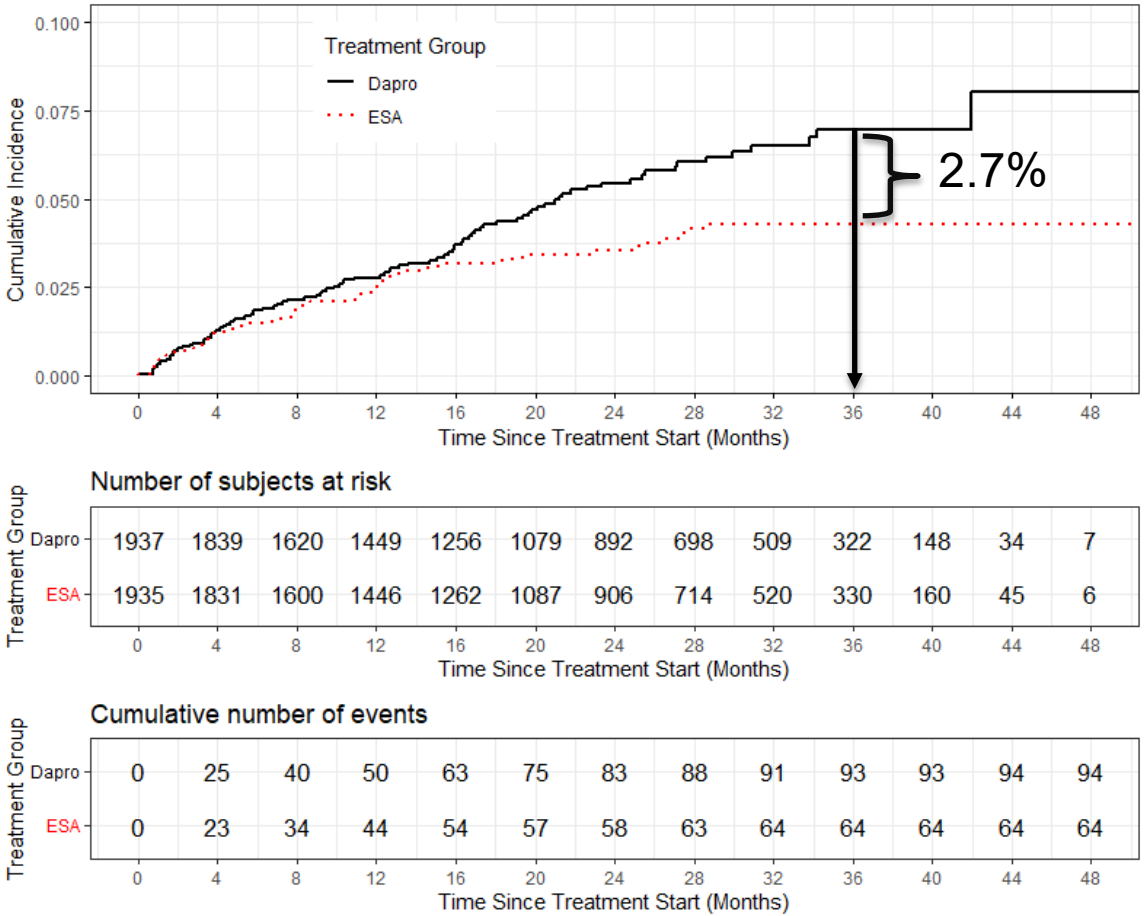
Rate Diff per 1000 PY (95% CI)	Hazard Ratio (95% CI)	**Rate Diff per 1000 PY (95% CI)**	Hazard Ratio (95% CI)
2 (-3 to 7)	1.16 (0.78, 1.73)	7 (3 to 12)	1.96 (1.24, 3.09)

Acute Kidney Injury - ASCEND-ND

Investigator-reported serious AEs showed a treatment difference, not favoring daprodustat

- Time to progression of CKD, a principal secondary endpoint, did not suggest harm
- No concerning trends in routine clinical laboratory assessments

AKI - ASCEND-ND

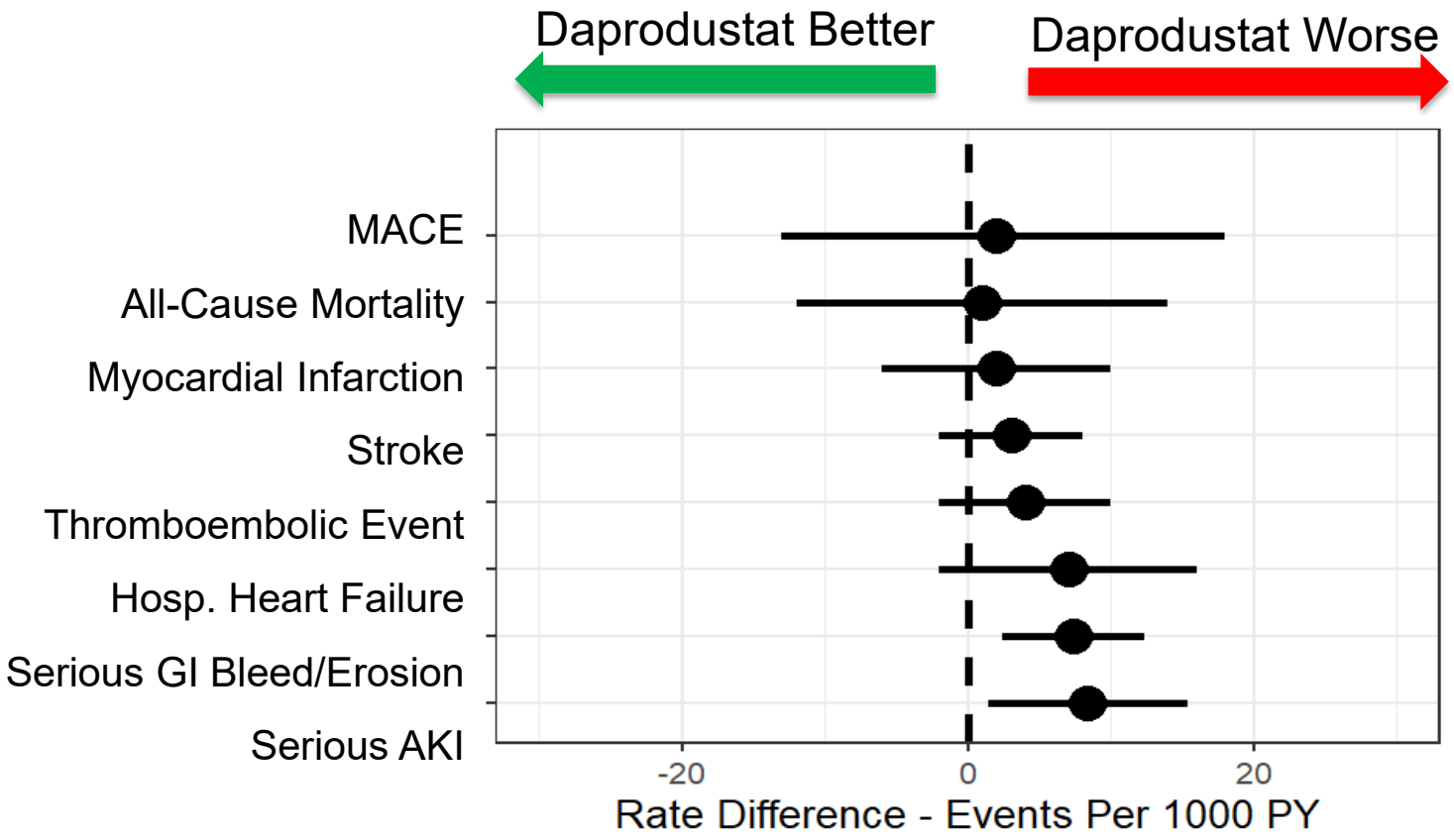


SUMMARY OF BENEFITS AND RISKS

Benefits of Daprodustat in ND and DD Populations

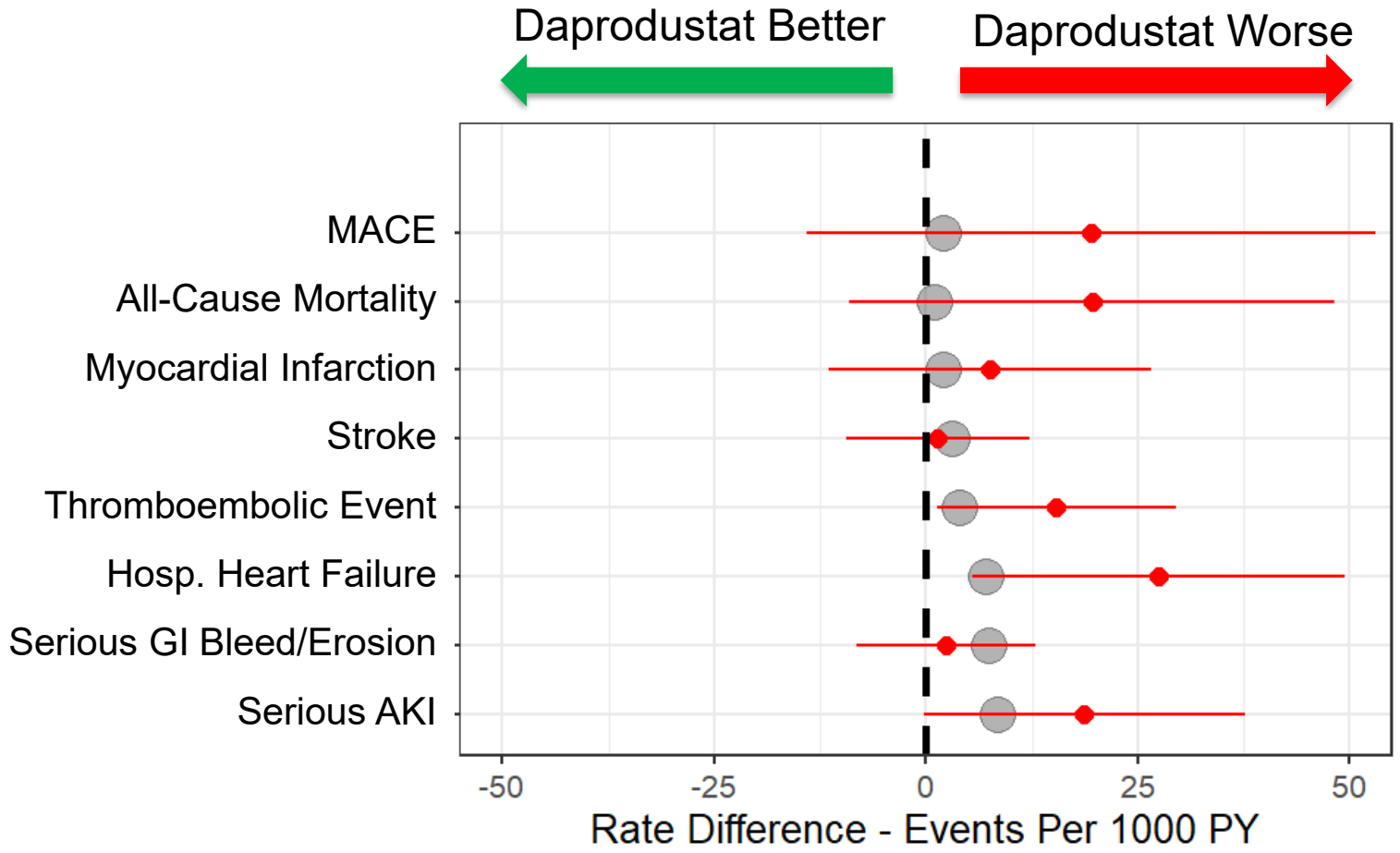
- Non-inferior to approved ESAs in increasing hemoglobin with continued need for RBC transfusions and rescue therapy
- Daprodustat is administered orally versus ESAs administered by injection; may provide some convenience over parenteral ESAs
  - Less clear advantage for patients who receive hemodialysis
  - Associated risk of inadequate Hb monitoring, which may lead to worse outcomes than demonstrated in trial setting

Summary of Risks in Non-Dialysis Population

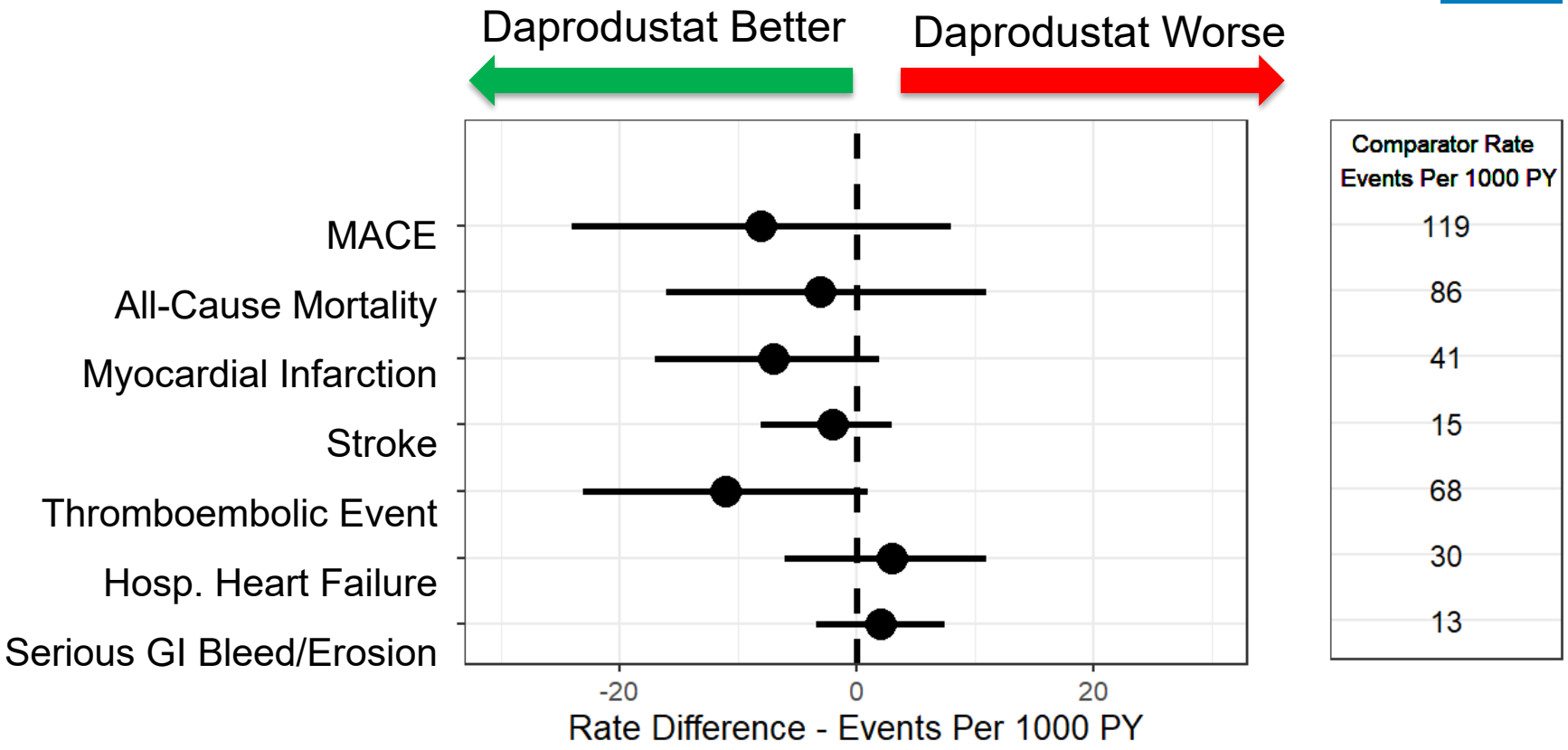


Comparator Rate Events Per 1000 PY
106
83
28
10
14
33
8
17

Summary of Risks in Non-Dialysis *U.S.* Population



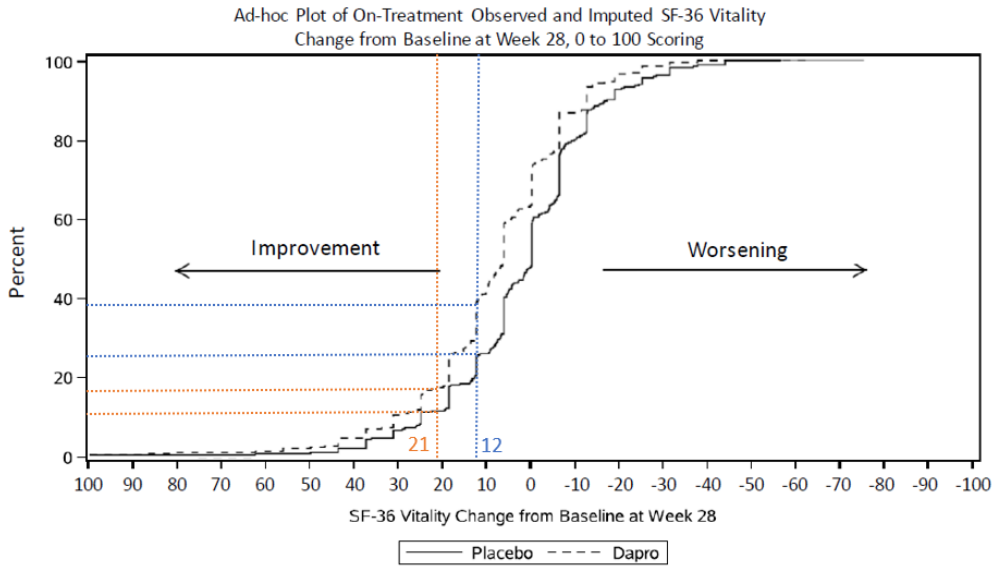
Summary of Risks in Dialysis Population



Additional Slides Shown

Clinical meaningfulness of PRO results

- The difference of patients achieving meaningful change is small between arms.



Threshold	Daprodustat N = 307	Placebo N = 307	Diff. from Treatment (95% CI)
≥ 12	121 (39%)	77 (25%)	12% (3%, 21%)
≥ 18	78 (25%)	54 (18%)	8% (0%, 16%)
≥ 21	52 (17%)	34 (11%)	6% (-1%, 14%)

Source: table created by PFSS based on Applicant's Study 205270 CSR Efficacy Data Source Tables-Post Hoc. Source Table 2.141 corresponds to a threshold of 12, Table 2.137 corresponds to a threshold of 18, and Table 2.138 corresponds to a threshold of 21.

Source: Sponsor's response to Information Request #42 dated September 19, 2022.

Clinical meaningfulness of PRO results

- The Applicant's proposed meaningful change threshold range: (6, 21).
- FDA considers the range of (18, 21) appropriate based on results of the anchor-based analysis (anchors: CKD-AQ Items 1 and 2) using data from Studies ASCEND-ND and ASCEND-ID.

  - **+ 6 points:** this threshold is based on changes observed in participants who had improved by +1 point on the PGI-S between Day 1 and Week 28 and changes observed among participants who reported being "very much improved" on the PGI-C at Week 28. +1 point improvements on the CKD-AQ Item 1 and 2 were 7.7 and 4.7 respectively and a moderate improvement on the PGI-C was 4.5. This threshold is also supported by consideration of mean and median definitions of meaningful change as reported in the research literature (Appendix 16).
  - **+ 12 points:** this threshold is based on changes observed in participants who had improved by +2 points on the PGI-S between Day 1 and Week 28.
  - **+ 18 points:** this threshold is based on participants who had improved by +2 points on CKD-AQ Item 2 (low energy) between Day 1 and Week 28.
  - **+21 points:** this threshold is based on participants who had improved by +2 points on CKD-AQ Item 1 (tiredness) between Day 1 and Week 28