



# Investor Science Event

Getting ahead of anaemia due to chronic kidney disease  
ASN Kidney Week 2021

7 November 2021

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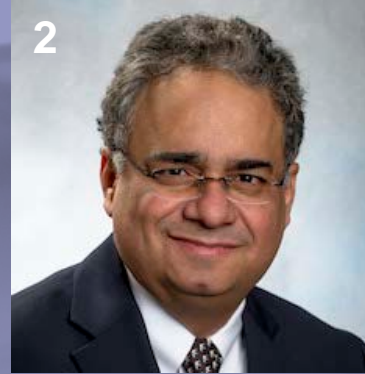
A number of adjusted measures are used to report the performance of our business, which are non-IFRS measures. These measures are defined and reconciliations to the nearest IFRS measure are available in our third quarter 2021 earnings release and Annual Report on Form 20-F for FY 2020.

All expectations and targets regarding future performance and the dividend should be read together with the section "Outlook, assumptions and cautionary statements" on pages 60 and 61 of our third quarter 2021 earnings release.

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## Speakers

1. Dr Hal Barron
2. Dr Ajay Singh
3. Luke Miels



# Agenda



**Daprodustat: a potential  
best-in-class treatment**

Dr Hal Barron

**ASCEND Phase III programme**

Dr Ajay Singh

**Commercial opportunity**

Luke Miels

**Q&A**

Dr Hal Barron  
Luke Miels  
Chris Corsico

Dr Ajay Singh  
John Lepore

# Daprodustat: a potential best-in-class treatment



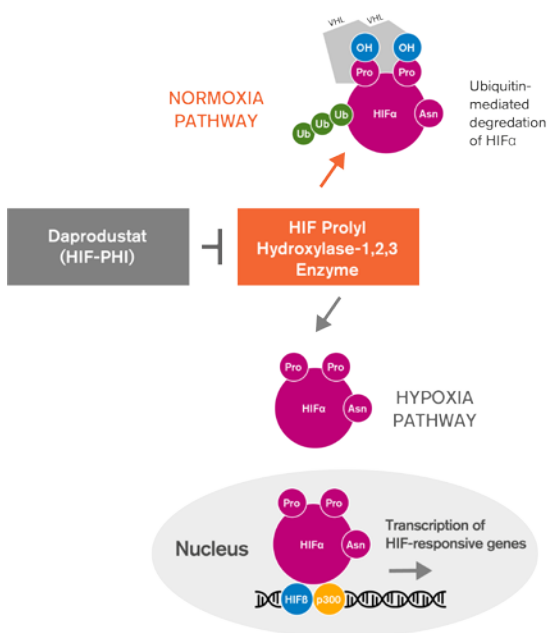
Dr Hal Barron, Chief Scientific Officer and President, R&D

# Daprodustat

Potential best-in-class treatment for patients with anaemia due to CKD<sup>1</sup>



## Nobel prize-winning science



## ASCEND<sup>2</sup>: Phase III clinical development programme with large geographical reach

- >8,000 patients with anaemia due to CKD<sup>3</sup> in five Phase III trials
- Consistent clinical trial programme:
  - Active control (injectable ESA<sup>4</sup>)
  - One global Hb<sup>5</sup> target range (10-11 g/dl)
  - Standardised patient management methods<sup>6</sup>
- Trial design and primary MACE<sup>7</sup> end-point aligned with global regulators
- No meta-analysis required
- Studies in dialysis (peritoneal, and haemodialysis) and non-dialysis

## High unmet medical need

**>700 million**

people suffer from chronic kidney disease worldwide<sup>8</sup>



One in seven patients suffer from anaemia of CKD where the current standard of care is administered via subcutaneous injection or as part of dialysis

1. Chronic kidney disease 2. Anaemia Studies in Chronic Kidney Disease: Erythropoiesis via a Novel prolyl hydroxylase inhibitor Daprodustat 3. Presented at American Society of Nephrology Kidney Week 2021: Singh AK, et al. FR-OR66 and PO0465; Coyne DM, et al PO0487; and Johansen KL, et al FR-CR53 4. Erythropoiesis-stimulating agents 5. Haemoglobin 6. Dose adjustment algorithms, iron management criteria and anaemia rescue algorithms 7. Evaluating a composite of all-cause mortality, stroke and myocardial infarction 8. *The Lancet*, The Global Burden of Chronic Kidney Disease published in February 2020.

# ASCEND Phase III programme



Dr Ajay K. Singh, Senior Associate Dean for Postgraduate Medical Education from Harvard Medical School, and Principal Investigator

# ASCEND Clinical Trial Program

The **A**nemia **S**tudies in **C**hronic Kidney Disease: **E**rythropoiesis via a **N**ovel prolyl hydroxylase inhibitor **D**aprodustat (**ASCEND**) Phase III program investigated the efficacy and safety profile of daprodustat across a spectrum of patients with CKD

Dialysis trials

Non-dialysis trials

**ascend/D**  
DIALYSIS

Cardiovascular  
Outcome Trials (CVOTs)

**ascend/ND**  
NON-DIALYSIS

**ascend/ID**  
INCIDENT DIALYSIS

ASCEND  
Phase III  
Program

**ascend/TD**  
THREE-TIMES WEEKLY  
DOSING IN DIALYSIS

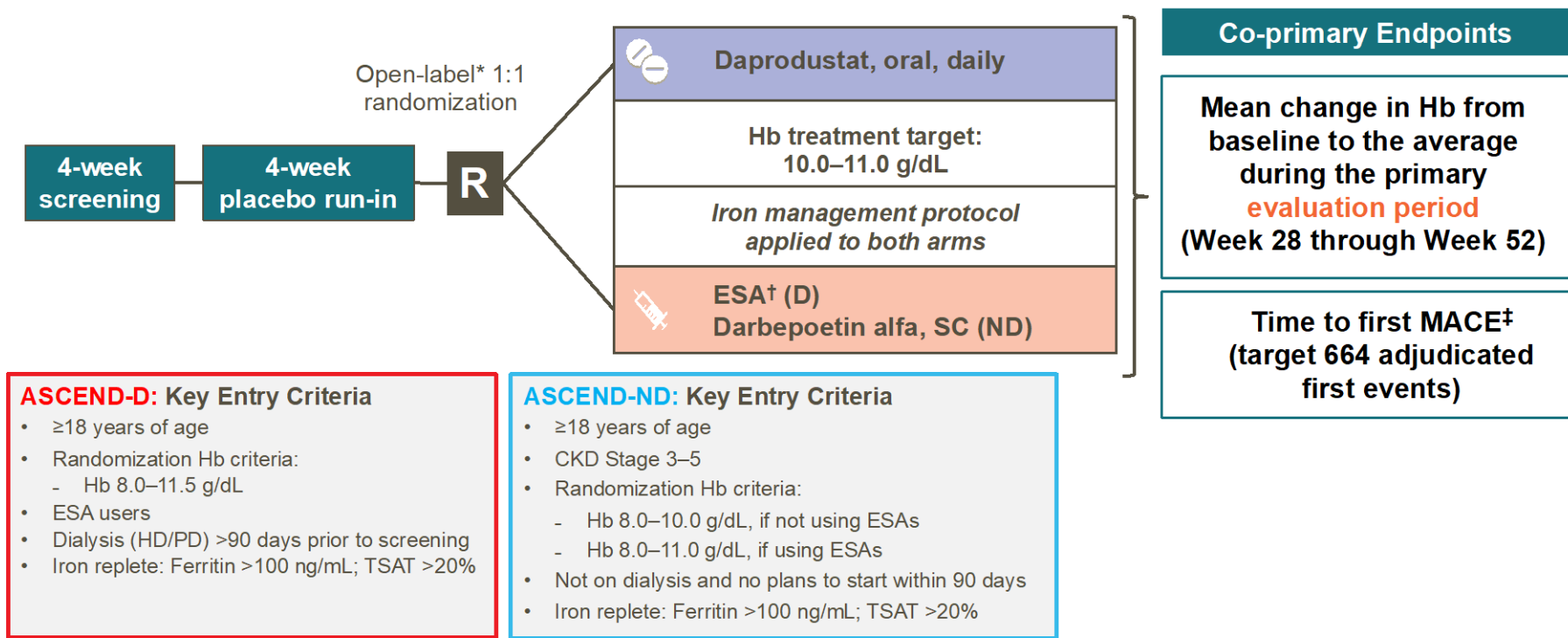
**ascend/NHQ**  
NON-DIALYSIS, HEMOGLOBIN  
& QUALITY OF LIFE



# ASCEND-D and -ND: Trial Design

Event-driven, open-label, randomized, active-controlled, parallel-group, multicenter, Phase 3 trials

ASCEND-D and ASCEND-ND accepted for publication



\*The sponsor, steering committee and endpoint adjudication committee remained blind to aggregate treatment assignment throughout the trial.

<sup>†</sup>Epoetin alfa (IV; HD patients) or darbepoetin alfa (SC; PD patients). <sup>‡</sup>MACE: composite of all-cause mortality, a non-fatal myocardial infarction, or a non-fatal stroke.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HD, hemodialysis; IV, intravenous; MACE, major adverse cardiovascular event; PD, peritoneal dialysis; R, randomization; SC, subcutaneous; TSAT, transferrin saturation.

# Patient Disposition

## ITT Population

Few patients withdrew and withdrawal rates were similar across treatment groups  
 Premature discontinuation of randomized treatment was balanced across treatment groups  
 Known vital status was high in both trials across both treatment groups

ascEND/D DIALYSIS/D	Daprodustat		ESA	ascEND/ND NON-DIALYSIS/ND	Daprodustat		Darbepoetin alfa
	Randomized, n	2964			Randomized, n	3872	
Intent-to-treat, n	1487		1477	Intent-to-treat, n	1937		1935
<b>Withdrew from trial, %</b>	<b>8</b>		<b>8</b>	<b>Withdrew from trial, %</b>	<b>3</b>		<b>3</b>
Completed the trial	92		92	Completed the trial	97		97
<b>Prematurely discontinued RT, %</b>	<b>53</b>		<b>53</b>	<b>Prematurely discontinued RT, %</b>	<b>38</b>		<b>38</b>
Did not prematurely discontinue RT	47		47	Did not prematurely discontinue RT	62		62
<b>Known vital status, %</b>	<b>98</b>		<b>98</b>	<b>Known vital status, %</b>	<b>99</b>		<b>99</b>
Unknown vital status	2		2	Unknown vital status	<1		<1

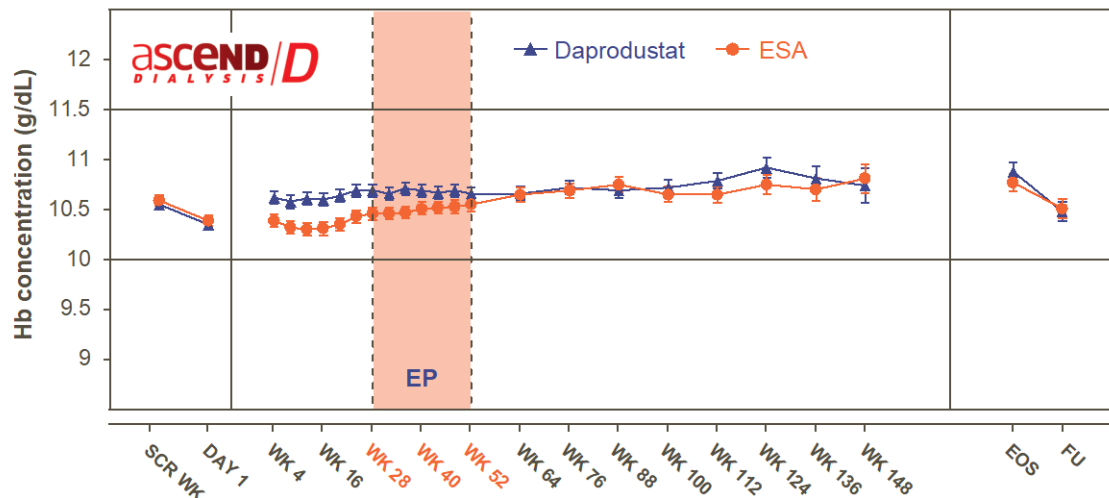
ITT, intent-to-treat; RT, randomized treatment.

Note: In ASCEND-D, 5 daprodustat and 3 ESA patients were randomized but never treated. In ASCEND-ND, 2 darbepoetin alfa patients were randomized but never treated.

# Co-primary Efficacy Endpoint: ASCEND-D

Mean Hb change from baseline to the **evaluation period** (Weeks 28–52) – ITT Population

Daprodustat was noninferior to ESA for mean change in Hb from baseline to the evaluation period (Weeks 28–52)



**Prespecified NI margin:**  
-0.75 g/dL

**Adjusted Mean Treatment Difference (95% CI)\***  
0.18 (0.12, 0.24)

**Noninferiority was achieved** because the lower limit of the 95% CI of the treatment difference was greater than the prespecified noninferiority margin of **-0.75 g/dL**

No. of patients

Daprodustat	1487	1485	1453	1403	1336	1274	1241	1191	1138	1092	1039	863	612	432	248	862	639
ESA	1477	1475	1449	1381	1323	1270	1225	1175	1125	1059	998	838	601	419	230	839	628

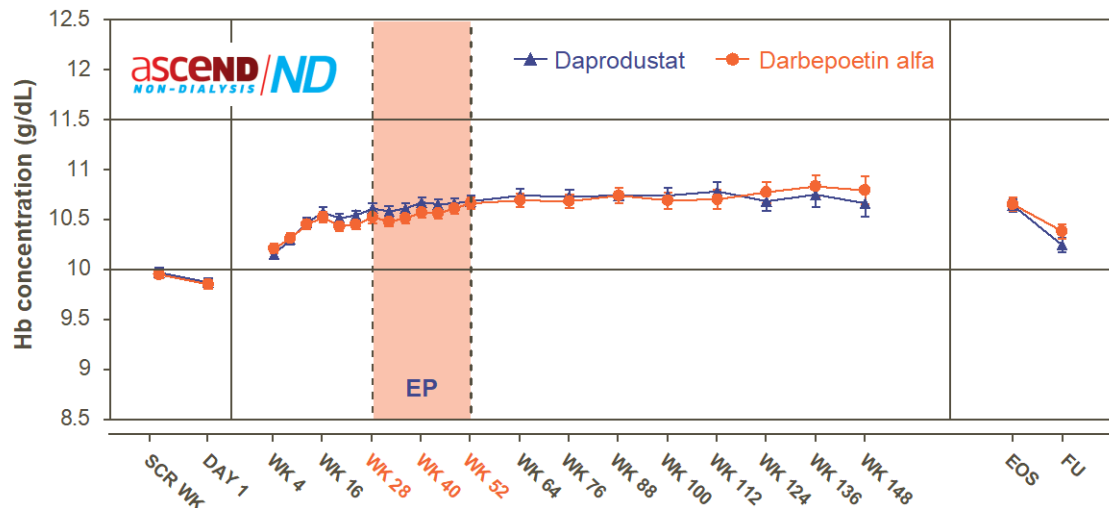
\*Based on an ANCOVA model using observed and imputed data with terms for treatment, baseline hemoglobin, dialysis type and region. Error bars indicate 95% CI. Post-randomization values include on- and off-treatment values. Visits on or before Day 1 include only pre-treatment values. Horizontal reference lines represent the Hb analysis range (10–11.5g/dL). The Hb target range for dose changes is 10–11g/dL. Vertical dotted lines represent the EP.

CI, confidence interval; EP, evaluation period; EOS, end of study; ESA, erythropoiesis-stimulating agent; FU, follow up; Hb, hemoglobin; ITT, intent-to-treat; NI noninferiority; SCR screening; Wk, week.

# Co-primary Efficacy Endpoint: ASCEND-ND

Mean Hb change from baseline to the **evaluation period** (Weeks 28–52) – ITT Population

Daprodustat was noninferior to darbepoetin alfa for mean change in Hb from baseline to the evaluation period (Weeks 28–52)



**Prespecified NI margin:**  
-0.75 g/dL

**Adjusted Mean Treatment Difference (95% CI)\***  
0.08 (0.03, 0.13)

**Noninferiority was achieved** because the lower limit of the 95% CI of the treatment difference was greater than the prespecified noninferiority margin of **-0.75 g/dL**

No. of patients

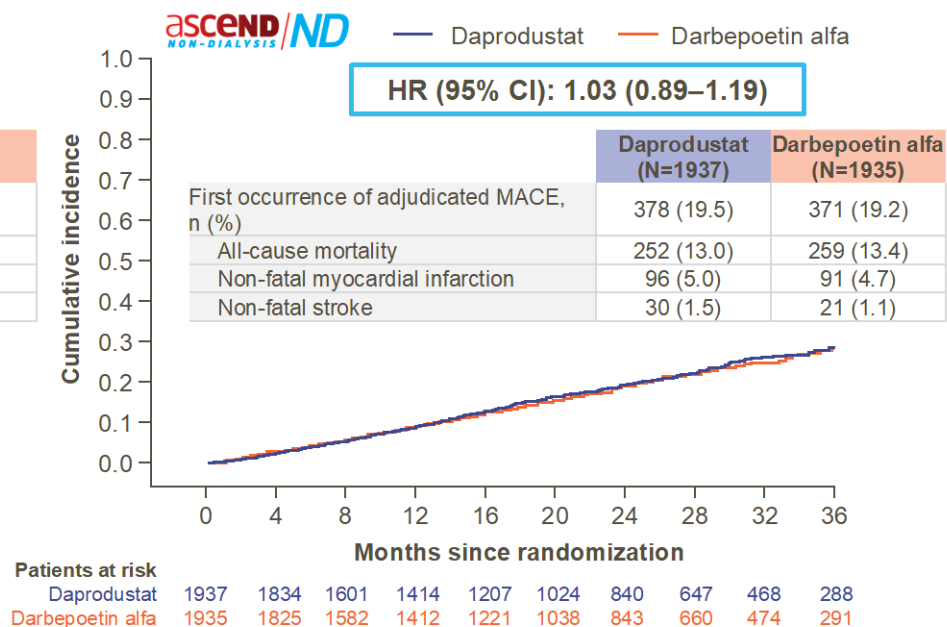
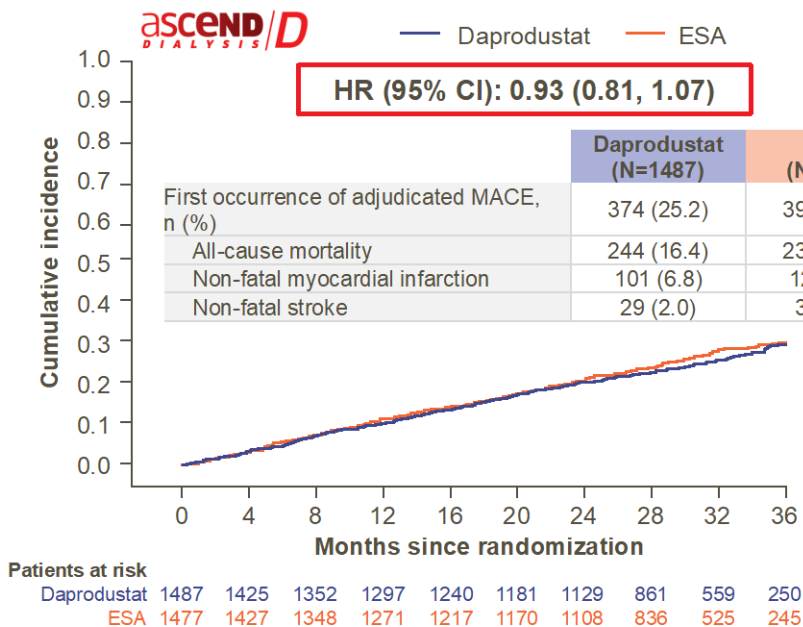
Daprodustat	1936	1932	1866	1705	1511	1364	1254	1100	961	832	725	587	453	349	243	1276	1056
Darbepoetin alfa	1935	1933	1867	1697	1506	1398	1243	1100	952	835	727	602	482	378	272	1278	1043

\*Based on an ANCOVA model using observed and imputed data with terms for treatment, baseline hemoglobin, current ESA use and region. Error bars indicate 95% CI. Post-randomization values include on- and off-treatment values. Visits on or before Day 1 include only pre-treatment values. Horizontal reference lines represent the Hb analysis range (10–11.5g/dL). The Hb target range for dose changes is 10–11g/dL. Vertical dotted lines represent the EP.

CI, confidence interval; EP, evaluation period; EOS, end of study; ESA, erythropoiesis-stimulating agent; FU, follow up; Hb, hemoglobin; ITT, intent-to-treat; NI noninferiority; SCR screening; Wk, week.

# First Occurrence of Adjudicated MACE

During the Time Period for Follow-up of CV Events – ITT Population

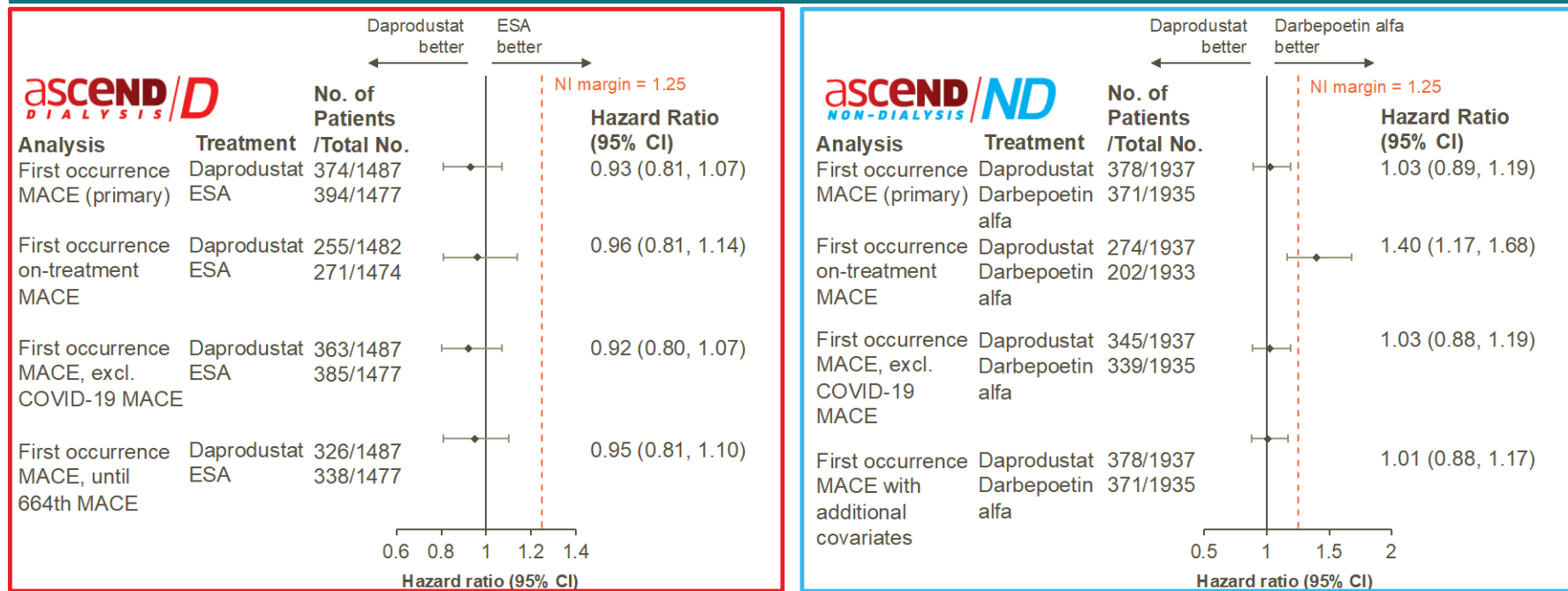


**Noninferiority was achieved** because the upper boundary of the 95% CI of the HR was lower than the pre-specified NI margin of 1.25

HR estimated using a Cox proportional hazards regression model with treatment group, dialysis type (ASCEND-D) or baseline ESA use (ASCEND-ND) and region as covariates. A HR <1 indicates a lower risk with daprodustat compared with ESA/darbeпоetin alfa. Note: y-axis scale may differ from those in the primary publications. CI, confidence interval; CV, cardiovascular; ESA, erythropoiesis-stimulating agent; HR, hazard ratio; ITT, intent-to-treat; MACE, major adverse cardiovascular event.

# MACE Supplementary Analyses



Supplementary MACE analyses were generally consistent with noninferiority conclusions from the primary analysis, except the ASCEND-ND on-treatment MACE analysis



Note: With the exception of the on-treatment analyses, all analyses follow the “ITT approach” and use both on- and off-treatment MACE events. On-treatment: from treatment start to the earlier of [28 days after the participant’s last dose of randomized treatment (last dose date + 28 days), or date of study completion/withdrawal]. HR estimated using a Cox proportional hazards regression model with treatment group, dialysis type (ASCEND-D) or baseline ESA use (ASCEND-ND) and region as covariates. A HR <1 indicates a lower risk with daprodustat compared with ESA/darbeoetin alfa. CI, confidence interval; ESA, erythropoiesis-stimulating agent; MACE, major adverse cardiovascular event; NI, noninferiority.

# Principal Secondary Endpoints

Principal secondary endpoints did not meet multiplicity-adjusted statistical significance for superiority\*



	Hazard ratio (95% CI) <sup>†</sup>		Hazard ratio (95% CI) <sup>†</sup>
MACE (superiority)	0.93 (0.81, 1.07)	MACE (superiority)	1.03 (0.89, 1.19)
MACE + thromboembolic events (DVT, PE, VAT)	0.88 (0.78, 1.00)	MACE + thromboembolic events (DVT, PE, VAT)	1.06 (0.93, 1.22)
MACE + hospitalization for heart failure	0.97 (0.85, 1.11)	MACE + hospitalization for heart failure	1.09 (0.95, 1.24)
	<b>Adjusted Mean Treatment Difference daprodustat-ESA (95% CI)<sup>‡</sup></b>		<b>Hazard ratio (95% CI)<sup>§</sup></b>
On-treatment average monthly IV iron dose (mg) from baseline to Week 52	-9.1 (-18.4, 0.2)	CKD progression (40% decline in eGFR OR ESRD, i.e., chronic dialysis, not initiating dialysis when indicated or kidney transplant)	0.98 (0.84, 1.13)

\*Holm-Bonferroni multiplicity adjustment used for principal secondary endpoints. <sup>†</sup>HR estimated using a Cox proportional hazards regression model with treatment group, dialysis type (ASCEND-D) or baseline ESA use (ASCEND-ND) and region as covariates. <sup>‡</sup>Based on an ANCOVA model with terms for treatment, baseline monthly IV iron dose, dialysis type and region; <sup>§</sup>Subdistribution hazard ratio estimated using Fine & Gray's proportional subdistribution hazard regression model with treatment group, baseline ESA use, and region as covariates. A HR <1 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa. CI, confidence interval; CKD, chronic kidney disease; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; ESRD, end stage renal disease; HR, hazard ratio; IV, intravenous; MACE, major adverse cardiovascular event; PE, pulmonary embolism; VAT, vascular access thrombosis.

# Adverse Events

Safety population reporting treatment-emergent events

**AE and SAE rates were similar between treatment groups in both studies**  
**Rates of AESIs were generally similar between treatment groups in both studies**

	Daprodustat (N=1482)	ESA (N=1474)		Daprodustat (N=1937)	Darbepoetin alfa (N=1933)
Rate of AEs	88%	85%	Rate of AEs	80%	77%
Rate of SAEs	52%	51%	Rate of SAEs	44%	36%

## Adverse Events of Special Interest (AESIs) undergoing further investigation:

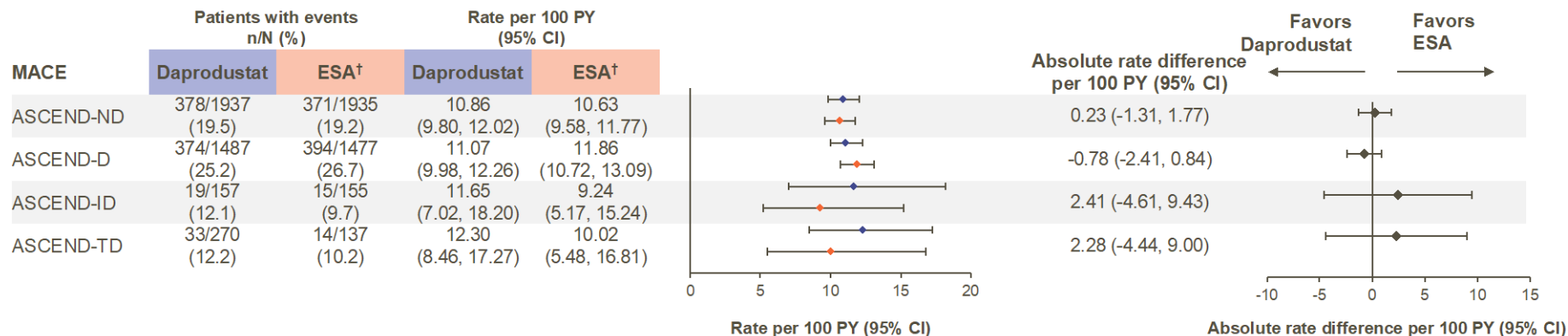
Esophageal and gastric erosions, % [n]	4.0% [60]	5.5% [81]	Esophageal and gastric erosions, % [n]	3.6% [70]	2.1% [41]
Cancer-related mortality and tumor progression and recurrence, % [n]	3.2% [47]	3.5% [51]	Cancer-related mortality and tumor progression and recurrence, % [n]	3.7% [72]	2.5% [49]

Safety population: all randomized patients who received at least one dose of randomized treatment. Treatment-emergent adverse events are reported which start or worsen on or after the participant's treatment start date and on or before the day after the participant's last dose of randomized treatment. Adverse events of special interest were investigator reported events and were not adjudicated. They were defined for daprodustat based on data from non-clinical and clinical studies, current information about HIF-associated pathophysiology, and identified risks for ESAs. A programmatic approach for these potential events was implemented using a broad set of terms of interest. AE, adverse event; AESI, adverse event of special interest; ESA, erythropoiesis-stimulating agent; HIF, hypoxia-inducible factor; SAE, serious adverse event.



# ASCEND Program-Level Cardiovascular Safety Data

MACE profile was generally consistent across treatment groups in all trials\*

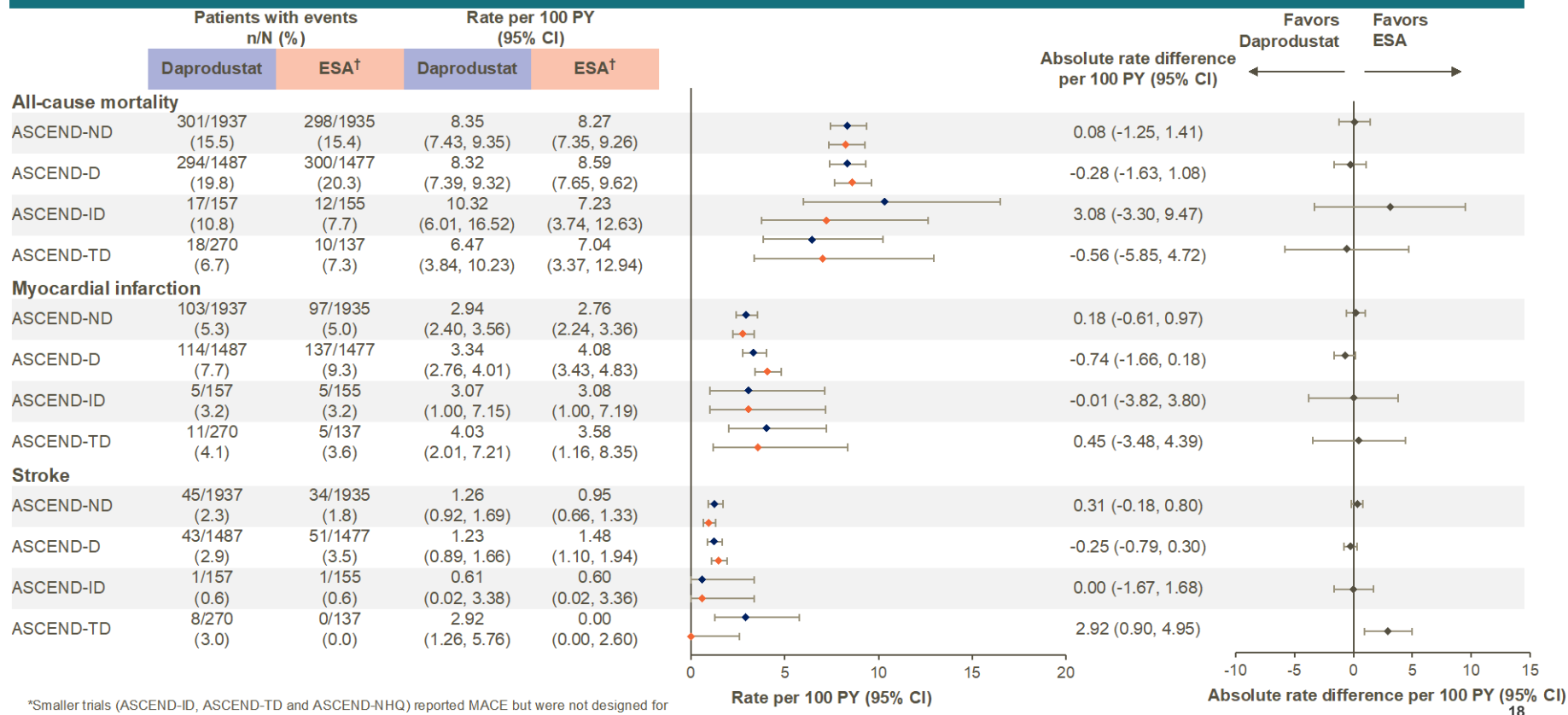


First MACE rates in ASCEND-NHQ (28 weeks): 4.9% daprodustat; 6.2% placebo

\*Smaller trials (ASCEND-ID, ASCEND-TD and ASCEND-NHQ) reported MACE but were not designed for formal MACE evaluation; †Darbepoetin alfa (ASCEND-D, -ND, -ID), epoetin alfa (ASCEND-D, -TD).

# ASCEND Program-Level Cardiovascular Safety Data

MACE components were generally consistent across treatment groups in all trials\*



\*Smaller trials (ASCEND-ID, ASCEND-TD and ASCEND-NHQ) reported MACE but were not designed for formal MACE evaluation; †Darbepoetin alfa (ASCEND-D, -ND, -ID), epoetin alfa (ASCEND-D, -TD).

# Summary and Conclusions

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- Daprodustat was as effective as conventional ESA therapy in treating anemia of CKD
- Daprodustat was noninferior to ESA with respect to CV safety and no new safety signals were observed

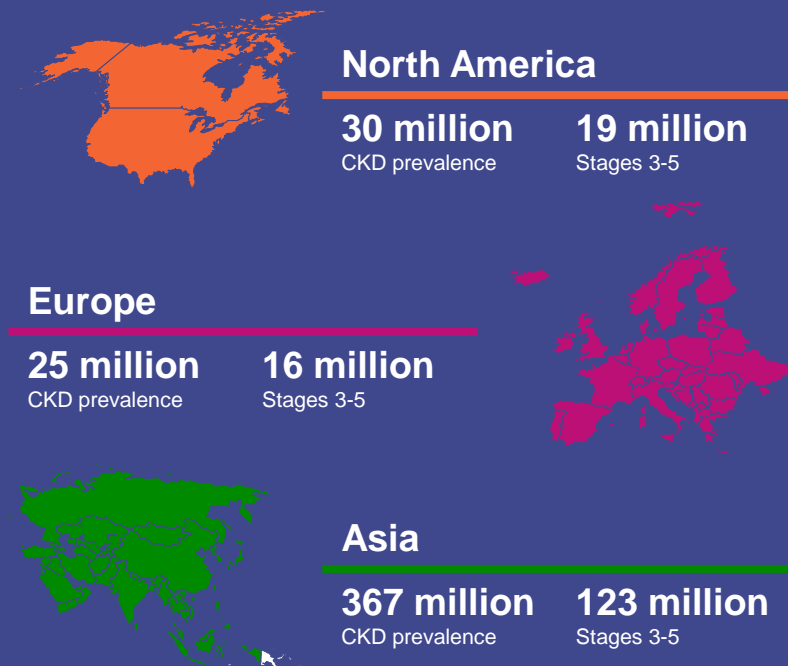
Daprodustat could represent an oral alternative to ESA for treating anemia of CKD  
in both dialysis and non-dialysis patients

# Commercial opportunity

Luke Miels, Chief Commercial Officer



# The prevalence of anaemia increases as CKD progresses; it is associated with an increased risk of hospitalisation, cardiovascular complications and death



## Treating patients with anaemia due to CKD

	Stage of CKD	Kidney function %	Diagnosed patients (m)	Average treatment duration (years)
Primary care physician and Nephrologist	Stage 3a	45-59	4.4	7.9
	Stage 3b	30-44	5.6	5.0
Nephrologist	Stage 4	15-29	1.3	4.2
	Stage 5	<15%	0.5	0.8

Source: 1. NHANES 2016 data accessed via Centers for Disease Control and Prevention, CKD Surveillance System—United States; website: <http://www.cdc.gov/ckd/>; 2. 2018 USRDS Annual data report— Volume 2: ESRD in the US 3. Lancet: Global, regional and national burden of chronic kidney disease, 1990–2017; 4. The prevalence of Chronic Kidney Disease in Asia, Liyanage T, Toyama T, ISN WCN 2020. 5 Spherix RealWorld Dynamix ND Patient Audit Neph and PCP – 2019; 6. GSK internal materials, 7. Dowling TC. Am J Health Syst Pharm 2007;64(13 Suppl 8):S3–7., Schmidt RJ, Dalton CL. Osteopath Med Prim Care 2007;1:14.

# HIF-PHI<sup>1</sup> class could become the new standard of care

Daprodustat has the potential to deliver patient benefit across populations



## Non-dialysis dependent

**>1 million**

Patients treated in the US and Europe

**c.30%**

Patients with Hb <10g/dl treated with ESA

**54%**

Treatment discontinuation in one year

## Dialysis dependent

**>850 thousand**

Patients treated in the US and Europe

**c.12%**

Patients treated with home dialysis  
(expected to grow to 25% by 2025)

**c.12%**

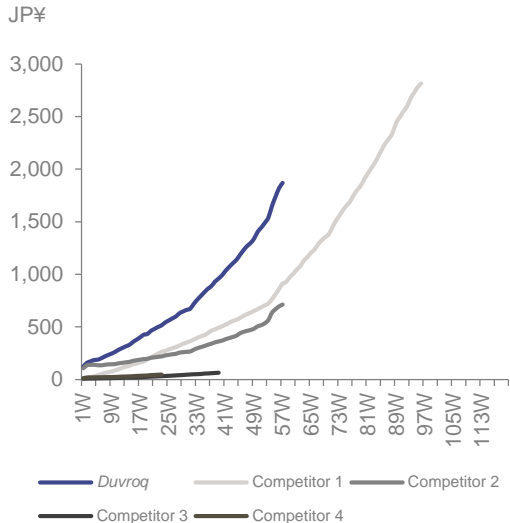
ESA hypo responders

1. Hypoxia-inducible factor prolyl hydroxylase Inhibitors. Source: Epidemiology data derived from multiple sources, including: 1. [https://www.thelancet.com/article/S0140-6736\(20\)30045-3/fulltext](https://www.thelancet.com/article/S0140-6736(20)30045-3/fulltext) 2. Prevalence of Anemia in Chronic Kidney Disease in the United States (nih.gov) 3. Nephrol Dial Transplant 2002, Suppl11:44-6 4. <https://www.nature.com/articles/s41598-020-79254-6>, 5CKDopps. Sci Rep 11, 1784 (2021). <https://doi.org/10.1038/s41598-020-79254-6>, Spherix RealWorld Dynamix 20Q2 report.

# Japan: *Duvroq* has achieved market-leading share

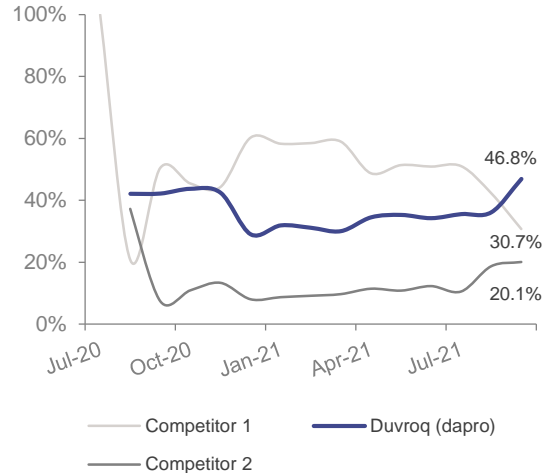


## Encouraging launch despite being second to market



Source: IQVIA JPM Monthly model, September flash data from IQVIA JPM flash.

## Leading market share



Source: IQVIA JPM Monthly model, September flash data from IQVIA JPM flash.

## Translating success in Japan to global expansion

### Strong momentum across populations

- 75% of patients switching from ESA to *Duvroq*
- 25% new to treatment

- Rx to patients in both DD (40%) and NDD (60%)

### Early engagement enabled smooth commercial transition

- Started early conversations with US commercial providers and large dialysis centers
- Encouraged by positive initial feedback and intent to include PHIs in treatment paradigm
- Will continue dialogue as we move closer to filing

# Daprodustat: an innovative, convenient oral treatment for patients with anaemia due to CKD



## Strong clinical data supports competitive commercial profile

- Convenient oral option for non-dialysis and dialysis patients
- Flexible dosing: QD<sup>1</sup> or TIW<sup>2</sup> with iron and phosphate binders
- Predictable Hb increase and maintenance within target level
- Improvements in QOL<sup>3</sup> including fatigue (SF-36 vitality score)

## Significant market opportunity

**>£2 billion**

US ESA CKD market

**>£1 billion**

Europe ESA CKD market

## Leveraging experience to deliver commercial success

- Investing behind internal capabilities
- >900 specialty experts hired since 2017
- Established leadership position with nephrologists from *Benlysta* LN launch

**H1 2022:** regulatory submissions (US, EU)

1. Once daily 2. Three times weekly 3. Quality of life.





# Q&A