HIF Stabilizer Trials in CKD/HD Patients – What Do the Data Really Show?

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DISCLOSURES

Affiliation/financial interest	Organization
Research grants	Argenx, Calliditas, Chinook Therapeutics, Galapagos, GSK, Novartis, Travere Therapeutics, Vera Therapeutics
Medical/scientific advisor	Alnylam Pharmaceuticals, Argenx, Astellas, Biocryst, Calliditas, Chinook Therapeutics, Dimerix, Galapagos, GSK, Novartis, Omeros, Travere Therapeutics, UCB, Vera Therapeutics, Visterra

HIF Stabilizer Trials in CKD/HD Patients

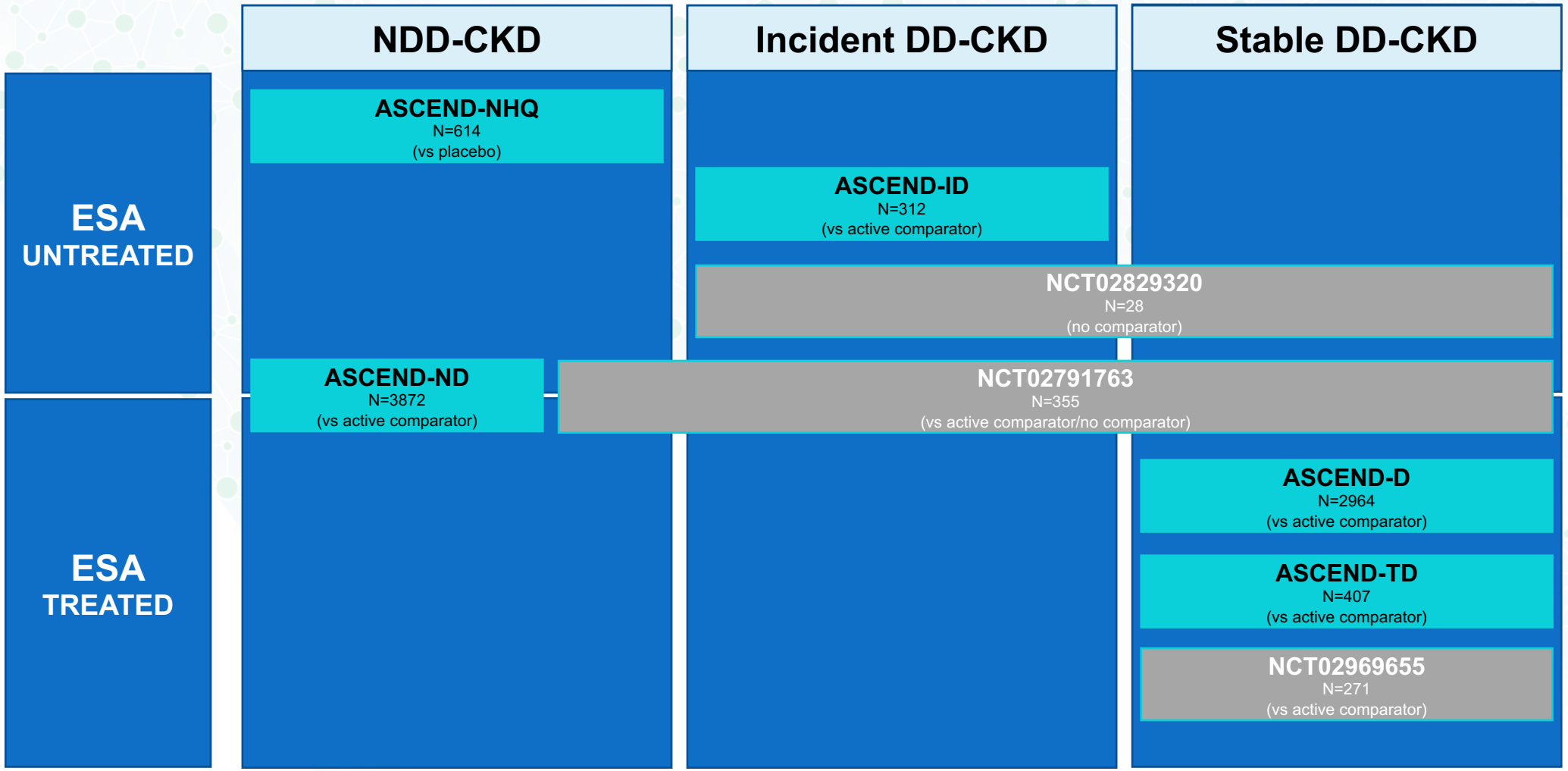
What Do the Data Really Show?

The Devil is in the Detail!

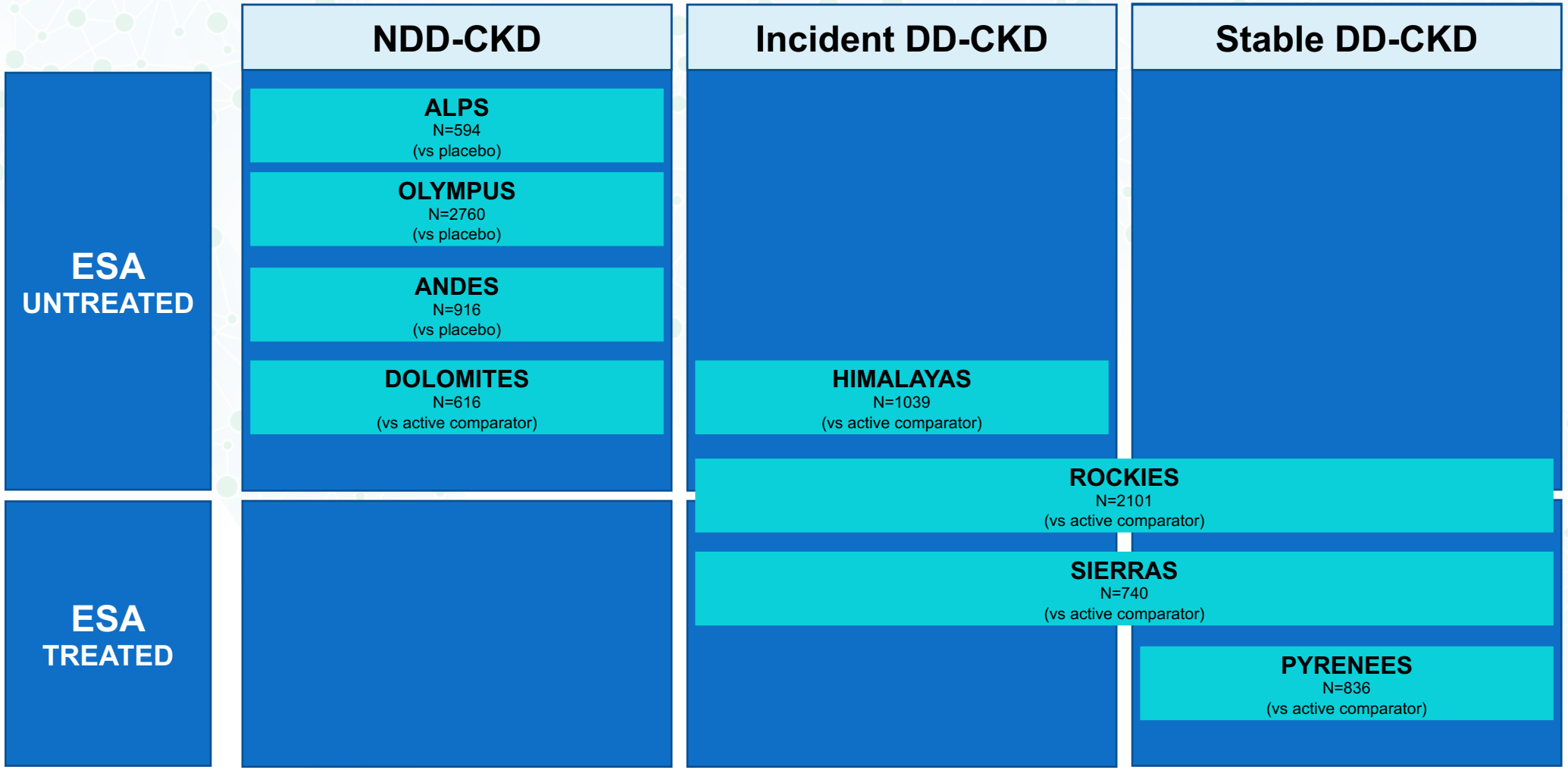
	Daprodustat	Roxadustat	Vadadustat
Manufacturer	GlaxoSmithKline	FibroGen/Astellas/AstraZeneca	Akebia Therapeutics
Geography	Global	Global	Global
Status	Approved Japan US & EU filing planned	Launched Chile, Japan, China, South Korea, Europe, UK US in process	Approved Japan US and EU filed
Half-life	4h	12-13h	4.5h
Expected dosing	Oral; QD	Oral; TIW	Oral; QD

	Daprodustat				Roxadustat				Vadadustat			
Global trial programme	**ASCEND**				**ALPINE**				**PRO$_2$TECT & INNO$_2$VATE**			
Trial population		NDD-CKD	INCIDENT DD-CKD	STABLE DD-CKD		NDD-CKD	INCIDENT DD-CKD	STABLE DD-CKD		NDD-CKD	INCIDENT DD-CKD	STABLE DD-CKD
	ESA UNTREATED	✓	✓		ESA UNTREATED	✓	✓		ESA UNTREATED	✓	✓	
	ESA TREATED	✓		✓	ESA TREATED	✓		✓	ESA TREATED	✓	✓	✓
Non-dialysis dependent population	Studies are against an active comparator/placebo and include conversion				Studies are placebo-controlled except for DOLOMITES Studies do not include conversion from ESA				Studies are against an active comparator and include conversion			
Comparator ESA	Darbepoetin alfa & rhEPO				Darbepoetin alfa & Epoetin alpha				Darbepoetin alfa			

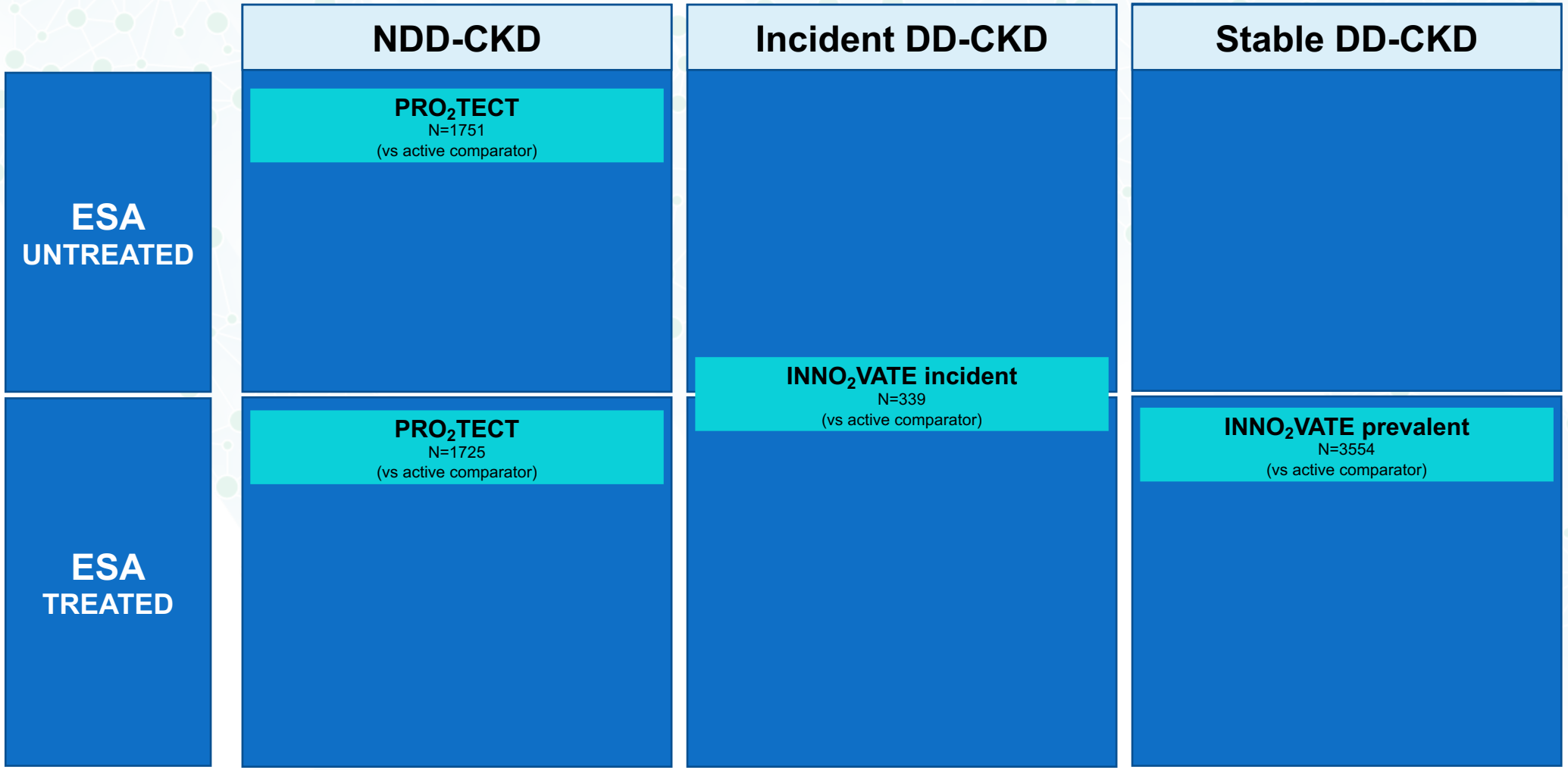
DAPRODUSTAT CLINICAL TRIAL OVERVIEW



ROXADUSTAT CLINICAL TRIAL OVERVIEW



VADADUSTAT CLINICAL TRIAL OVERVIEW



The Devil is in the Detail!

All global programs but relative contribution of different regions is variable between studies & programs

Patient phenotype by region may differ:

- ethnicity
- starting Hb
- co-morbidities
- concomitant medications

Efficacy/Safety (cardiovascular & thromboembolic risk) analytical approaches:

- Non-inferiority vs superiority approaches vary
- Sensitivity analyses vary
- Reliability of non-inferiority in small subgroups

Efficacy/Safety profile (cardiovascular & thromboembolic risk) likely to vary depending on:

- NDD, IDD & SDD
- Prior ESA exposure?
- Does the ESA comparator matter?

Class effects vs drug-specific effects:

- efficacy
- safety

NDD-CKD: Placebo-controlled studies

	Daprodustat ASCEND-NHQ	Roxadustat ALPS, OLYMPUS, ANDES	Vadadustat
Size	614	4,270	
Comparator	placebo	placebo	
Correction/conversion	Hb correction	Hb correction	
Treatment period	28 weeks	52 weeks-4 years	
Evaluation period	Wks 24-28	Wks 28-52	
Primary Endpoints	Change from BL in Hb averaged over Wks 24-28	Change from BL in Hb averaged over Wks 28-52 (US) Hb response during first 24 weeks of therapy, without rescue therapy (EU)	
Target Hb	11.0-12.0 g/dL	≥11.0 g/dL	
MACE		Pooled NDD placebo-controlled CV analysis	
Additional key endpoints	Time to rescue therapy QoL (CKD-AQ, SF-36, PGI-S, WPAI-ANS-CPV, EQ-5D-5L, EQ-VAS) BP/MAP change BP exacerbation	Time to rescue therapy IV iron use eGFR rate of change LDL cholesterol change QoL (SF-36) MAP change Time to worsened HTN	

The Devil is in the Detail!

What impact do the following have on the evaluation of efficacy & safety?

- treatment period
- evaluation period
- target Hb
  - US vs ex-US
- definition of primary outcome
  - US vs ex-US
- reported secondary outcomes & their definitions
  - patient reported outcomes/assessment of QoL

NDD-CKD:ESA-CONTROLLED STUDIES

	Daprodustat ASCEND-ND	Roxadustat DOLOMITES	Vadadustat PRO$_2$TECT (2 trials)
Size	3,872 (53% ESA-untreated)	616	1,751 (ESA-untreated); 1725 (ESA-treated)
Comparator	Darbepoetin alfa	Darbepoetin alfa	Darbepoetin alfa
Correction/conversion	Hb correction & ESA conversion	Hb correction	Hb correction & ESA conversion
Treatment period	52 weeks- end of study	Up to 104 weeks	52 weeks-end of treatment
Evaluation period	Wks 28-52	Wks 28-36	Wks 24-36
Primary Endpoints	Change from BL in Hb averaged over Wks 28-52 First occurrence of a MACE	Hb response during first 24 weeks of therapy, without rescue therapy	Change from BL in Hb averaged over Wks 24-36 First occurrence of a MACE
Target Hb	10.0-11.0 g/dL	≥11.0 g/dL	10.0-11.0 g/dL (US) 10.0-12.0 g/dL (ex-US)
MACE	Yes	Yes	Yes
Additional key endpoints	CKD progression eGFR change QoL (CKD-AQ, SF-36, PGI-S, EQ-5D-5L) MACE or thromboembolic event MACE or hospitalisation Time to thromboembolic events ACM, CV mortality, fatal or non-fatal MI, fatal or non-fatal stroke BP exacerbations BP/MAP change	Time to first IV iron use LDL cholesterol change QoL (SF-36, FACT-An, EQ-5D-5L) MAP change Time to first occurrence of HTN	IV iron use RBC transfusion CKD progression ESA rescue Expanded MACE CV death, non-fatal MI or nonfatal stroke CV death ACM

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What impact do the following have on the evaluation of efficacy & safety?

- treatment period
- evaluation period
- target Hb
  - US vs ex-US
- definition of primary outcome
  - US vs ex-US
- reported secondary outcomes & their definitions
  - patient reported outcomes/assessment of QoL
- correction vs conversion
  - ESA conversion factor used
  - magnitude of correction
  - rate of correction

INCIDENT DD-CKD:ESA-CONTROLLED STUDIES

	Daprodustat ASCEND-ID	Roxadustat HIMALAYAS, ROCKIES, SIERRAS	Vadadustat INNO$_2$VATE incident
Size	312	1,530	369
Comparator	Darbepoetin alfa	Epoetin alfa	Darbepoetin alfa
Correction/conversion	Hb correction	Hb correction (Himalayas & Rockies) ESA conversion (Sierras)	ESA conversion
Treatment period	52 weeks	52 weeks-4 years	52 weeks-end of treatment
Evaluation period	Wks 28-52	Wks 28-52	Wks 24-36
Primary Endpoints	Change from BL in Hb averaged over Wks 28-52	Change from BL in Hb averaged over Wks 28-52 regardless of rescue therapy (Rockies & Sierras) Hb response during first 24 weeks without rescue therapy (Himalayas)	Change from BL in Hb averaged over Wks 24-36 First occurrence of a MACE
Target Hb	10.0-11.0 g/dL	$\geq$11.0 g/dL (Himalayas) 11 $\pm$ 1 g/dL (Rockies & Sierras)	10.0-11.0 g/dL (US) 10.0-12.0 g/dL (ex-US)
MACE		Pooled CV analysis	Yes
Additional key endpoints	IV iron use BP exacerbation BP/MAP change QoL (CKD-AQ, SF-36, PGI-S, EQ-5D-5L)	IV iron use LDL cholesterol change RBC transfusion MAP change Exacerbation of HTN Rescue therapy use	IV iron use RBC transfusion Expanded MACE CV death, non-fatal MI or nonfatal stroke CV death ACM

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- treatment period
- evaluation period
- target Hb
  - US vs ex-US
- definition of primary outcome
  - US vs ex-US
- reported secondary outcomes & their definitions
  - patient reported outcomes/assessment of QoL
- correction vs conversion
  - ESA conversion factor used
  - magnitude of correction
  - rate of correction
- pros & cons of pooled analyses
- how do we view data in iron usage…..

STABLE DD-CKD:ESA-CONTROLLED STUDIES

	Daprodustat ASCEND-D	Roxadustat PYRENEES, ROCKIES,SIERRAS	Vadadustat INNO$_2$VATE prevalent
Size	2,964	3,188	3,554
Comparator	Epoetin alfa or Darbepoetin alfa	Epoetin alfa or Darbepoetin alfa	Darbepoetin alfa
Correction/conversion	ESA conversion (ESA responders and non-responders)	ESA conversion (ESA responders only-stable dose for 4 weeks)	ESA conversion
Treatment period	52 weeks-end of study	52 weeks-4 years	52 weeks-end of treatment
Evaluation period	Wks 28-52	Wks 28-36; Wks 28-52	Wks 24-36
Primary Endpoints	Change from BL in Hb averaged over Wks 28-52 First occurrence of a MACE	Change from BL in Hb averaged over Wks 28-52 regardless of rescue therapy Change from BL in Hb averaged over Wks 28-36 without rescue therapy (Pyrenees)	Change from BL in Hb averaged over Wks 24-36 First occurrence of a MACE
Target Hb	10.0-11.0 g/dL	11 $\pm$ 1 g/dL (Rockies & Sierras) 10.0-12.0 g/dL (Pyrenees)	10.0-11.0 g/dL (US) 10.0-12.0 g/dL (ex-US)
MACE	Yes	Pooled CV analysis	Yes
Additional key endpoints	IV iron use Change in BP Time to rescue QoL (SF-36, PGI-S, EQ-5D-5L) MACE or thromboembolic event MACE or hospitalization for HF ACM, CV mortality, fatal or non-fatal MI, fatal or non-fatal stroke	IV iron use LDL cholesterol change RBC transfusion MAP change Exacerbation of HTN Time to increase in BP QoL (SF-36, FACT-An, EQ-5D-5L, PGIC)	IV iron use RBC transfusion Expanded MACE CV death, non-fatal MI or nonfatal stroke CV death ACM

The Devil is in the Detail!

What impact do the following have on the evaluation of efficacy & safety?

- treatment period
- evaluation period
- target Hb
  - US vs ex-US
- definition of primary outcome
  - US vs ex-US
- reported secondary outcomes & their definitions
  - patient reported outcomes/assessment of QoL
- correction vs conversion
  - ESA conversion factor used
  - magnitude of correction
  - rate of correction
- pros & cons of pooled analyses
- how do we view data in iron usage…..
- ESA responders vs non-responders
- dialysis vintage

EFFICACY: HB RESPONSE

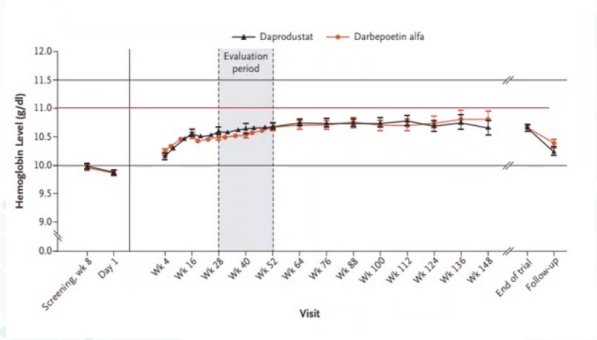
NDD-CKD:ESA-CONTROLLED STUDIES

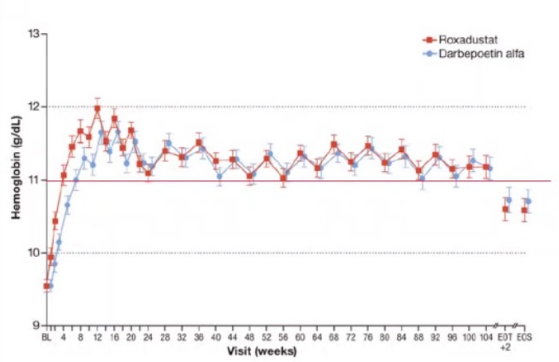
	Daprodustat **ASCEND-ND** **N=3,872**	**Roxadustat** **DOLOMITES** **N=616**	**Vadadustat** **PRO$_2$TECT** **ESA-untreated=1,751; ESA-treated=1,725**
Mean baseline Hb	DAPRO 9.9 g/dL; DA 9.8 g/dL	ROXA 9.55 g/dL; DA 9.55 g/dL	ESA-untreated 9.1 g/dL ESA-treated 10.4 g/dL (both treatment groups)
Target Hb	10.0-11.0 g/dL	≥ 11.0 g/dL	10.0-11.0 g/dL (US) 10.0-12.0 g/dL (ex-US)
Hb change from baseline	**Change from baseline in Hb to Wks 28-52 (g/dL)** DAPRO: 0.74 vs DA: 0.66 **non-inferiority**	**Change from baseline in Hb to Wks 28-36 (g/dL)** ROXA: 1.85 vs DA: 1.84	**Change from baseline in Hb to Wks 24-36 (g/dL)** VADA: 1.43 vs DA: 1.38 **non-inferiority**
Hb response		**Hb response during first 24 weeks of therapy** ROXA: 89.5% vs DA 78.0% **non-inferiority**	

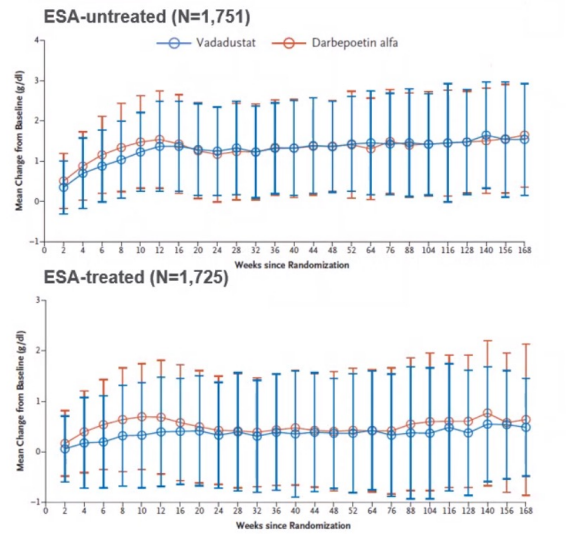
EFFICACY: HB RESPONSE

NDD-CKD:ESA-CONTROLLED STUDIES

Daprodustat	Roxadustat	Vadadustat
ASCEND-ND N=3,872	DOLOMITES N=616	PRO_2TECT ESA-untreated=1,751; ESA-treated=1,725







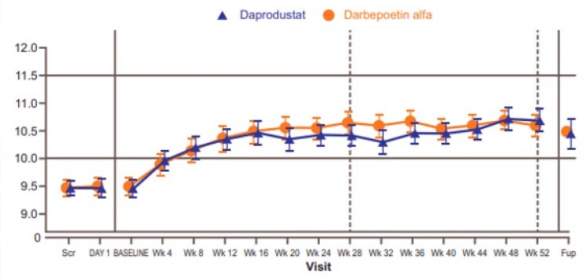
EFFICACY: HB RESPONSE
INCIDENT DD-CKD:ESA-CONTROLLED STUDIES

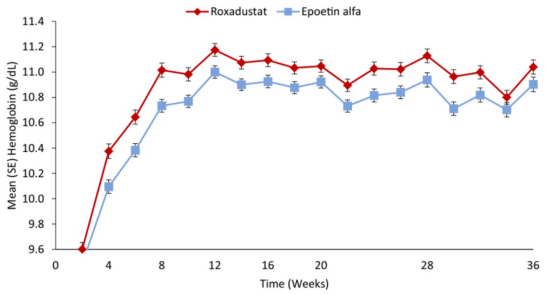
	Daprodustat ASCEND-ID N=312	Roxadustat HIMALAYAS, ROCKIES, SIERRAS N=1,530	Vadadustat INNO$_2$VATE incident N=369
Mean baseline Hb	DAPRO 9.5 g/dL; DA 9.5 g/dL	ROXA 8.8 g/dL; ESA 8.9 g/dL	VADA 9.4 g/dL; DA 9.2 g/dL
Target Hb	10.0-11.0 g/dL	≥11.0 g/dL (Himalayas) 11 ± 1 g/dL (Rockies & Sierras)	10.0-11.0 g/dL (US) 10.0-12.0 g/dL (ex-US)
Hb change from baseline	**Change from baseline in Hb to Wks 28-52 (g/dL)** AMD: -0.10 (95% CI: -0.34, 0.14)	**Change from baseline in Hb to Wks 28-52 (g/dL)** ROXA: 2.12 vs ESA: 1.91 **(pooled analysis)**	**Change from baseline in Hb to Wks 24-36 (g/dL)** VADA: 1.26 vs DA: 1.58 **non-inferiority (pooled analysis)**
Hb response		**Hb response during weeks 28-52** ROXA: 59.9% vs ESA 59.6%	**Hb response during weeks 24-36** VADA: 43.6% vs DA: 56.9% **Hb response during weeks 40-52** VADA: 39.8% vs DA: 41.0%

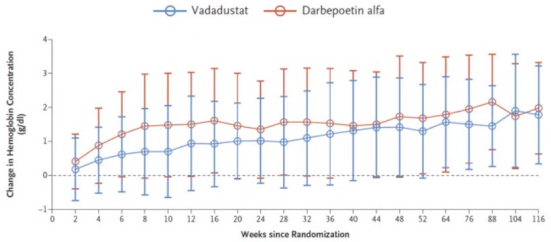
EFFICACY: HB RESPONSE

INCIDENT DD-CKD:ESA-CONTROLLED STUDIES

Daprodustat	Roxadustat	Vadadustat
ASCEND-ID	HIMALAYAS, ROCKIES, SIERRAS	INNO$_2$VATE incident
N=312	N=1,530	N=369







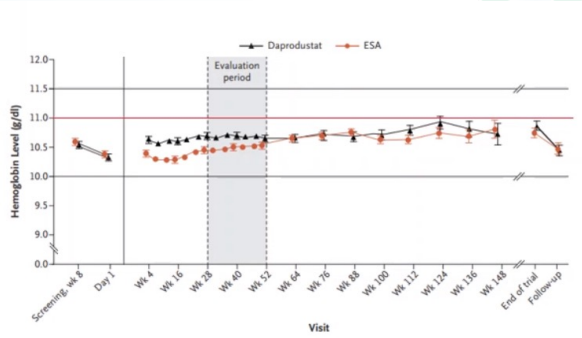
EFFICACY: HB RESPONSE
STABLE DD-CKD:ESA-CONTROLLED STUDIES

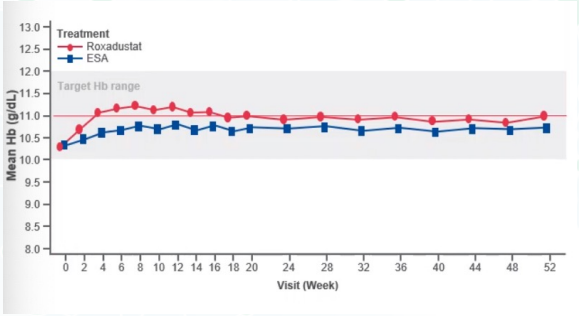
	Daprodustat **ASCEND-D** **N=2,964**	**Roxadustat** **PYRENEES, ROCKIES, SIERRAS** **N=3,188**	**Vadadustat** **INNO$_2$VATE prevalent** **N=3,554**
Mean baseline Hb	DAPRO 10.4 g/dL; DA 10.4 g/dL	ROXA 10.3 g/dL; ESA 10.4 g/dL	VADA 10.6 g/dL; DA 10.2 g/dL
Target Hb	10.0-11.0 g/dL	10.0-12.0 g/dL (Pyrenees) 11 ± 1 g/dL (Rockies & Sierras)	10.0-11.0 g/dL (US) 10.0-12.0 g/dL (ex-US)
Hb change from baseline	**Change from baseline in Hb to Wks 28-52 (g/dL)** DAPRO: 0.28 VS ESA: 0.1 **non-inferiority**	**Change from baseline in Hb to Wks 28-36 (g/dL)** ROXA: 0.65 vs ESA: 0.36 **(pooled analysis)**	**Change from baseline in Hb to Wks 24-36 (g/dL)** VADA: 1.26 vs DA: 1.58 **non-inferiority (pooled)**
Hb response		**Hb response during weeks 28-36** ROXA: 70.9% vs ESA 67.7%	**Hb response during weeks 24-36** VADA: 49.2% vs DA: 53.2% **Hb response during weeks 40-52** VADA: 44.3% vs DA: 50.9%

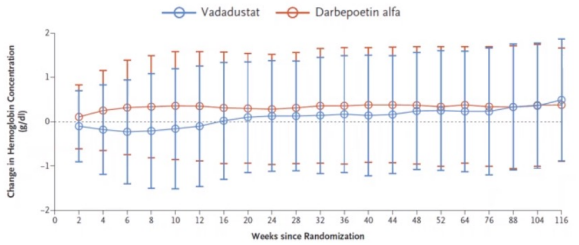
EFFICACY: HB RESPONSE

STABLE DD-CKD:ESA-CONTROLLED STUDIES

Daprodustat	Roxadustat	Vadadustat
ASCEND-D	PYRENEES, ROCKIES, SIERRAS	INNO$_2$VATE prevalent
N=2,964	N=3,188	N=3,554







EFFICACY: CHANGE IN IV IRON USE

ESA-CONTROLLED STUDIES

	Daprodustat ASCEND-ND N=3,872	Roxadustat DOLOMITES N=616	Vadadustat PRO$_2$TECT ESA-untreated=1,751; ESA-treated=1,725
NDD population	**Patients with IV iron use during Wks 24-36** DAPRO: 11% vs DA: 10%	**Patients with IV iron use during Wks 1-36** ROXA: 6.2% vs DA: 12.7% (HR: 0.45; 95% CI: 0.26, 0.78); p=0.004	**Patients with ≥1 administration of IV iron:** **Wks 24-36** VADA: 8.6% vs DA: 9.0% (ESA-untreated) VADA: 7.4% vs DA: 5.5% (ESA-treated) **Wks 40-52** VADA: 10.8% vs DA: 10.5% (ESA-untreated) VADA: 9.5% vs DA: 5.4% (ESA-treated)
	Daprodustat **ASCEND-ID** **N=312**	**Roxadustat** **HIMALAYAS, ROCKIES, SIERRAS** **N=1,530**	**Vadadustat** **INNO$_2$VATE incident** **N=369**
IDD population	**Mean monthly IV iron dose to Wk 52** DAPRO vs DA AMD: 19.4 mg/month (95% CI: -11.0, 49.9)	**Mean monthly IV iron dose over Wks 28-52** ROXA: 53.6 mg vs ESA: 70.2 mg/patient exposure months; P<0.0001	**Patients with ≥1 administration of IV iron:** **Wks 24-36** VADA: 69.9% vs DA: 64.5% **Wks 40-52** VADA: 63.2% vs DA: 62.1%
	Daprodustat **ASCEND-D** **N=2,964**	**Roxadustat** **PYRENEES, ROCKIES, SIERRAS** **N=3,188**	**Vadadustat** **INNO$_2$VATE prevalent** **N=3,554**
SDD population	**Mean monthly IV iron dose to Wk 52** DAPRO: 90.8 mg vs ESA: 99.9 mg (Mean difference: -9.1; 95% CI: -18.4, 0.2)	**Mean monthly IV iron dose over Wks 28-52** ROXA: 42.5 mg vs ESA: 62.0 mg/patient exposure months	**Patients with ≥1 administration of IV iron:** **Wks 24-36** VADA: 56.0% vs DA: 56.0% **Wks 40-52** VADA: 58.5% vs DA: 58.9%

THE DEVIL IS IN THE DETAIL!

What impact do the following have on the evaluation of efficacy & safety?

- treatment period
- evaluation period
- target Hb
  - US vs ex-US
- definition of primary outcome
  - US vs ex-US
- reported secondary outcomes & their definitions
  - patient reported outcomes/assessment of QoL
- correction vs conversion
  - ESA conversion factor used
  - magnitude of correction
  - rate of correction
- pros & cons of pooled analyses
- how do we view data in iron usage…..
- ESA responders vs non-responders
- dialysis vintage

- Definition of iron replete/deficient
- Protocolised use of iron supplementation
- Target iron parameters

EFFICACY: QUALITY OF LIFE & SYMPTOMS

NDD population (placebo-controlled)	Daprodustat ASCEND-NHQ N=614	Roxadustat ALPS, OLYMPUS, ANDES N=4,270	Vadadustat
	≥6 point increase in SF-36 vitality score to Wk 28 DAPRO: 58% vs PBO: 40%; P=0.0049	Olympus Study: superiority of ROXA to PBO for SF-36 Vitality Score at Wk 12 (HR: 0.22; 95% CI: 0.15, 2.3)	
NDD population (ESA-controlled)	**Daprodustat ASCEND-ND N=614**	**Roxadustat DOLOMITES N=616**	**Vadadustat PRO_2TECT ESA-untreated=1,751; ESA-treated=1,725**
		Non-inferiority of ROXA to DA for SF-36 Physical Function and SF-36 Vitality Score	
IDD population (ESA-controlled)	**Daprodustat ASCEND-ID N=312**	**Roxadustat HIMALAYAS, ROCKIES, SIERRAS N=1,530**	**Vadadustat $INNO_2VATE$ incident N=369**
	Non-inferiority		
SDD population (ESA-controlled)	**Daprodustat ASCEND-D N=2,964**	**Roxadustat PYRENEES, ROCKIES, SIERRAS N=3,188**	**Vadadustat $INNO_2VATE$ prevalent N=3,554**
		Pyrenees Study: non-inferiority of ROXA to ESA for SF-36 Physical Function and SF-36 Vitality Score changes from BL to weeks 12 to 28	

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- correction vs conversion
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- how do we view data in iron usage…..
- ESA responders vs non-responders
- dialysis vintage

- What is the right tool?
- When is the right time to assess QoL?
- The same tool for NDD & DD patients?

- Definition of iron replete/deficient
- Protocolised use of iron supplementation
- Target iron parameters

TOP LEVEL SAFETY: MACE

NDD-CKD: PLACEBO-CONTROLLED STUDIES

	Daprodustat **ASCEND-NHQ** **N=614**	**Roxadustat** **ALPS, OLYMPUS, ANDES** **N=4,270**		**Vadadustat**
	Hb correction	Hb correction		
		ROXA	PBO	
MACE (OT)		14.4%	8.8%	
		HR: 1.26 (95% CI: 1.02, 1.55)		
MACE+ (OT)		18.8%	12.8%	
		HR: 1.17 (95% CI: 0.99, 1.40)		
ACM (OT)		10.9%	6.5%	
		HR: 1.16 (95% CI: 0.90, 1.50)		
MACE (ITT)		20.1%	18.6%	
		HR: 1.10 (95% CI: 0.96, 1.27)		
MACE+ (ITT)		24.2%	22.9%	
		HR: 1.07 (95% CI: 0.94, 1.21)		
ACM (ITT)		16.8%	16%	
		HR: 1.08 (95% CI: 0.93, 1.26)		

The Devil is in the Detail!

What impact do the following have on the evaluation of efficacy & safety?

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- target Hb
  - US vs ex-US
- definition of primary outcome
  - US vs ex-US
- reported secondary outcomes & their definitions
  - patient reported outcomes/assessment of QoL
- correction vs conversion
  - ESA conversion factor used
  - magnitude of correction
  - rate of correction
- pros & cons of pooled analyses
- how do we view data in iron usage…..
- ESA responders vs non-responders
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- Intention to Treat analyses or the On Treatment analyses?

- What is the right tool?
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- Target iron parameters

TOP LEVEL SAFETY: MACE

NDD-CKD:ESA-CONTROLLED STUDIES

	Daprodustat ASCEND-ND N=3,872		Roxadustat DOLOMITES N=616		Vadadustat PRO$_2$TECT ESA-untreated=1,751; ESA-treated=1,725	
	Hb correction & ESA conversion		Hb correction		Hb correction & ESA conversion	
	DAPRO	DA	ROXA	PBO	VADA	DA
MACE	19.5%	19.2%	11.8%	14.0%	22%	19.9%
	non-inferiority		HR: 0.89 (95% CI: 0.60, 1.33) (ITT) HR: 0.81 (95% CI: 0.52, 1.25) (OT)		did not meet non-inferiority margin	
Secondary MACE endpoint	**MACE or thromboembolic event**		**MACE+**		**Expanded MACE**	
	21.8%	20.9%	16.7%	18.1%	25.9%	24.5%
	HR: 1.06 (95% CI: 0.93, 1.22)		HR: 0.90 (95% CI: 0.61, 1.32)		HR: 1.11 (95% CI: 0.97, 1.27)	
	MACE or hospitalisation for heart failure					
	22.9%	21.6%				
	HR: 1.09 (95% CI: 0.95, 1.24)					
Death Any Cause	13.0%	13.4%	9.0%	10.6%	18.3%	17.7%
Nonfatal MI	5.0%	4.7%	3.4%	3.4%	3.9%	2.8%
Nonfatal stroke	1.5%	1.1%	1.2%	2.4%	2.0%	1.6%

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What impact do the following have on the evaluation of efficacy & safety?

- treatment period
- evaluation period
- target Hb
  - US vs ex-US
- definition of primary outcome
  - US vs ex-US
- reported secondary outcomes & their definitions
  - patient reported outcomes/assessment of QoL
- correction vs conversion
  - ESA conversion factor used
  - magnitude of correction
  - rate of correction
- pros & cons of pooled analyses
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TOP LEVEL SAFETY: MACE
INCIDENT DD-CKD:ESA-CONTROLLED STUDIES

	Daprodustat **ASCEND-ID** **N=312**		**Roxadustat** **HIMALAYAS, ROCKIES, SIERRAS** **N=1,530**		**Vadadustat** **INNO$_2$VATE incident** **N=369**	
	Hb correction		Hb correction (Himalayas, Rockies) ESA conversion (Sierras)		Hb correction & ESA conversion	
	DAPRO	DA	ROXA	DA	VADA	DA
MACE	12.1%	9.7%	9.7%	12.7%	12.3%	12.9%
			HR: 0.83 (95% CI: 0.61, 1.13)		**non-inferiority (pooled)**	
Secondary MACE endpoint			**MACE+**		**Expanded MACE (incident & stable pooled)**	
			11.6%	15.8%	21.6%	23.0%
			HR: 0.76 (95% CI: 0.57, 1.00)		HR: 0.96 (95% CI: 0.84, 1.10)	
ACM			6.8%	9.1%		
			HR: 0.83 (95% CI: 0.57, 1.19)			
Death Any Cause	8.9%	5.8%			13.0% (pooled)	12.9% (pooled)
Nonfatal MI	3.2%	3.2%			3.9% (pooled)	4.5% (pooled)
Nonfatal stroke	0.0%	0.6%			1.3% (pooled)	1.9% (pooled)

TOP LEVEL SAFETY: MACE

STABLE DD-CKD:ESA-CONTROLLED STUDIES

	Daprodustat **ASCEND-D** **N=2,964**		**Roxadustat** **PYRENEES, ROCKIES, SIERRAS** **N=3,188**		**Vadadustat** **INNO$_2$VATE prevalent** **N=3,554**	
	ESA conversion (ESA responders and non-responders)		ESA conversion (ESA responders only-stable dose for 4 weeks)		ESA conversion	
	DAPRO	DA	ROXA	DA	VADA	DA
MACE	25.2%	26.7%	18.6%	18.9%	18.8%	20.0%
	non-inferiority		HR: 1.18 (95% CI: 1.00, 1.38)		**non-inferiority (pooled)**	
Secondary MACE endpoint	**MACE or thromboembolic event**		**MACE+**		**Expanded MACE (incident & stable pooled)**	
	33.4%	36.8%	22.4%	25.3%	21.6%	23.0%
	HR: 0.88 (95% CI: 0.78, 1.00)		HR: 1.03 (95% CI: 0.90, 1.19)		HR: 0.96 (95% CI: 0.84, 1.10)	
	MACE or hospitalisation for heart failure					
	28.6%	29.3%				
	HR: 0.97 (95% CI: 0.85, 1.11)					
ACM			13.3%	13.0%		
			HR: 1.23 (95% CI: 1.02, 1.49)			
Death Any Cause	16.4%	15.8%			13.0% (pooled)	12.9% (pooled)
Nonfatal MI	6.8%	8.5%			3.9% (pooled)	4.5% (pooled)
Nonfatal stroke	2.0%	2.4%			1.3% (pooled)	1.9% (pooled)

TOP LEVEL SAFETY: THROMBOEMBOLIC EVENTS

NDD population (placebo-controlled)	Daprodustat ASCEND-NHQ N=614	Roxadustat ALPS, OLYMPUS, ANDES N=4,270	Vadadustat
		PE: ROXA 0.4%; PBO 0.2% **DVT:** ROXA 1.0%; PBO 0.2%	
NDD population (ESA-controlled)	**Daprodustat ASCEND-ND N=3,872**	**Roxadustat DOLOMITES N=616**	**Vadadustat PRO$_2$TECT ESA-untreated=1,751; ESA-treated=1,725**
	Nonfatal TEE: DAPRO 3.0% VS 2.4% **VAT:** DAPRO 2.1%; DA 1.5% **PE:** DAPRO 0.3%; DA 0.0% **DVT:** DAPRO 0.7%; DA 0.9%	**DVT/PE:** ROXA 2.5%; DA 0.7%	**ANY FIRST TEE:** VADA 1.9%; DA 2.2% **VAT:** VADA 0.7%; DA 0.8% **PE:** VADA 0.3%; DA 0.2% **DVT:** VADA 0.9%; DA 1.2%
IDD population (ESA-controlled)	**Daprodustat ASCEND-ID N=312**	**Roxadustat HIMALAYAS, ROCKIES, SIERRAS N=1,530**	**Vadadustat INNO$_2$VATE incident & prevalent pooled N=3,923**
		VAT:ROXA 10.4%; ESA 8.7% **PE:** ROXA 0.4%; ESA 0.4% **DVT:** ROXA 0.5%; ESA 0.5%	**VAT:** VADA 7.5%; DA 6.1% **PE:** VADA 0.3%; DA 0.5% **DVT:** VADA 0.8%; DA 1.0% **ANY FIRST TEE:** VADA 8.7%; DA 7.6%
SDD population (ESA-controlled)	**Daprodustat ASCEND-D N=2,964**	**Roxadustat PYRENEES, ROCKIES, SIERRAS N=3,188**	
	VAT: DAPRO 10.4%; DA 12.5% **PE:** DAPRO 0.1%; DA 0.3% **DVT:** DAPRO 1.0%; DA 0.9% **Nonfatal TEE:** DAPRO 11.5% VS 13.7%	**VAT:**ROXA 13.9%; ESA 10.9% **PE:** ROXA 0.6%; ESA 0.6% **DVT:** ROXA 1.7%; ESA 0.2%	

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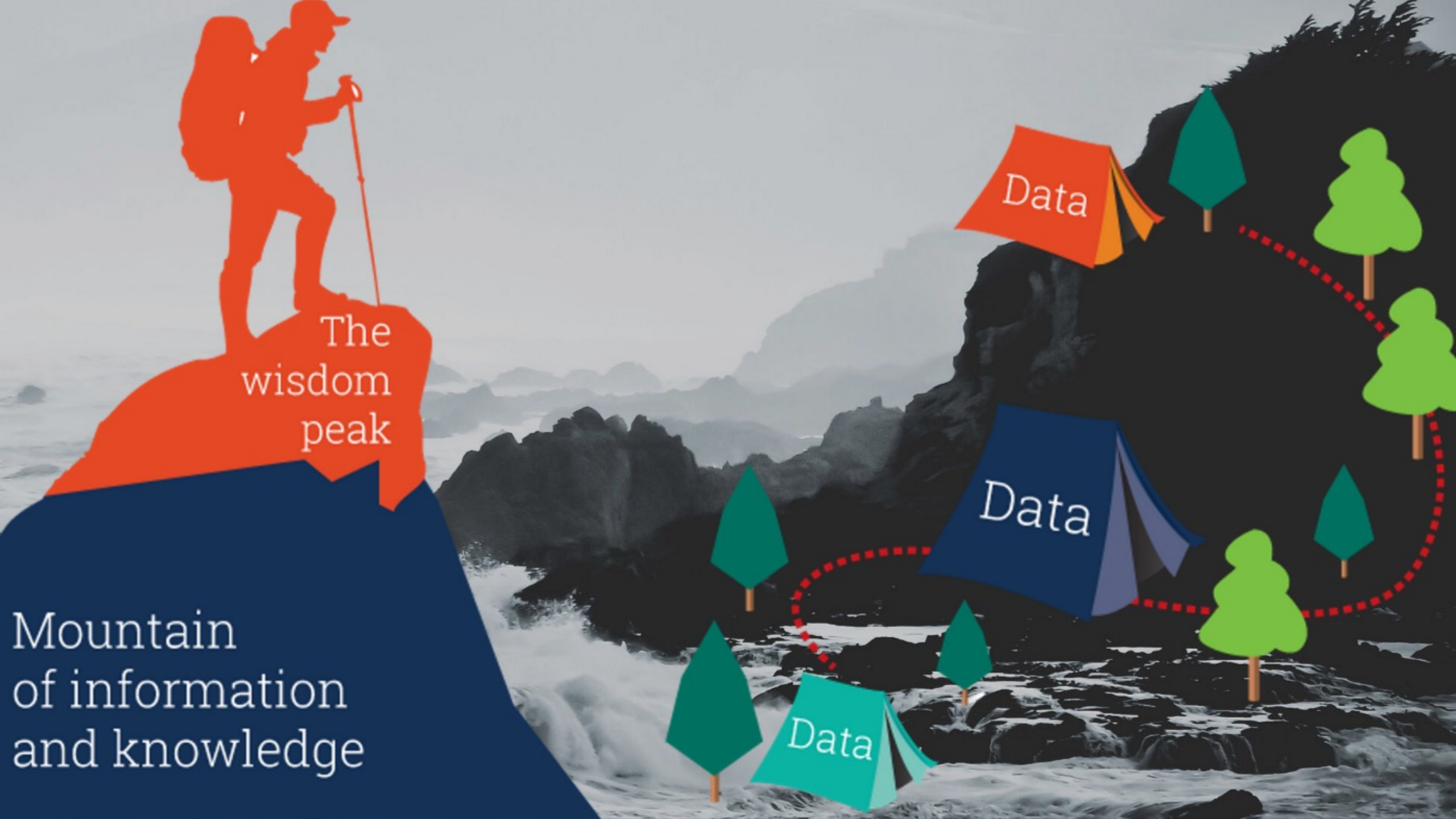
The wisdom peak
Data
Data
Data
Mountain of information and knowledge