STARTS-1 and -2

A randomized, double-blind,16 week placebo controlled, dose ranging, parallel group study of oral monotherapy sildenafil in treatment naive children, aged 1-17 years, with pulmonary arterial hypertension (PAH). STARTS-1 was followed by sildenafil dose extension study STARTS-2

Barst R, Ivy DD, et al. Circulation 2012;125:324-334

Disclosures

- The University of Colorado contracts with Actelion, Gilead, Pfizer, United Therapeutics for Dr Ivy to be a consultant
- Investigator Initiated grants: Gilead
- Steering Committee: GSK / Actelion

STARTS-1 Study Criteria

- **Inclusion**
  - Aged 1-17 years with PAH (WHO Group 1)
  - IPAH, HPAH, APAH-CHD, PAH-CTD
  - ≥ 8 kg
  - $VO_{2\ Peak}$ ≥10 mL/kg/min and ≤28 mL/kg/min
- **Exclusion**
  - **Unrepaired CHD with systemic arterial oxygen saturation <88%**
  - **ERA / Prostanoid / Nitrate /PDE-5 / L-arginine**

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STARTS-1 Objectives & Endpoints

- **Primary efficacy endpoint**

  - Percentage change from baseline in peak VO_2 at Week 16

- **Secondary efficacy endpoints**

  - Change from baseline in mean pulmonary artery pressure (mPAP)

  - Change from baseline in pulmonary vascular resistance index (PVRI)

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STARTS-1 Study Design – Treatment Allocation

	Placebo	Low Dose		Medium Dose		High Dose	
Body Weight(kg)	Allocation Ratio	Dose	Allocation Ratio	Dose	Allocation Ratio	Dose	Allocation Ratio
≥8 - 20	1			10 mg	1	20 mg	2
>20 - 45	1	10 mg	1	20 mg	1	40 mg	1
>45	1	10 mg	1	40 mg	1	80 mg	1

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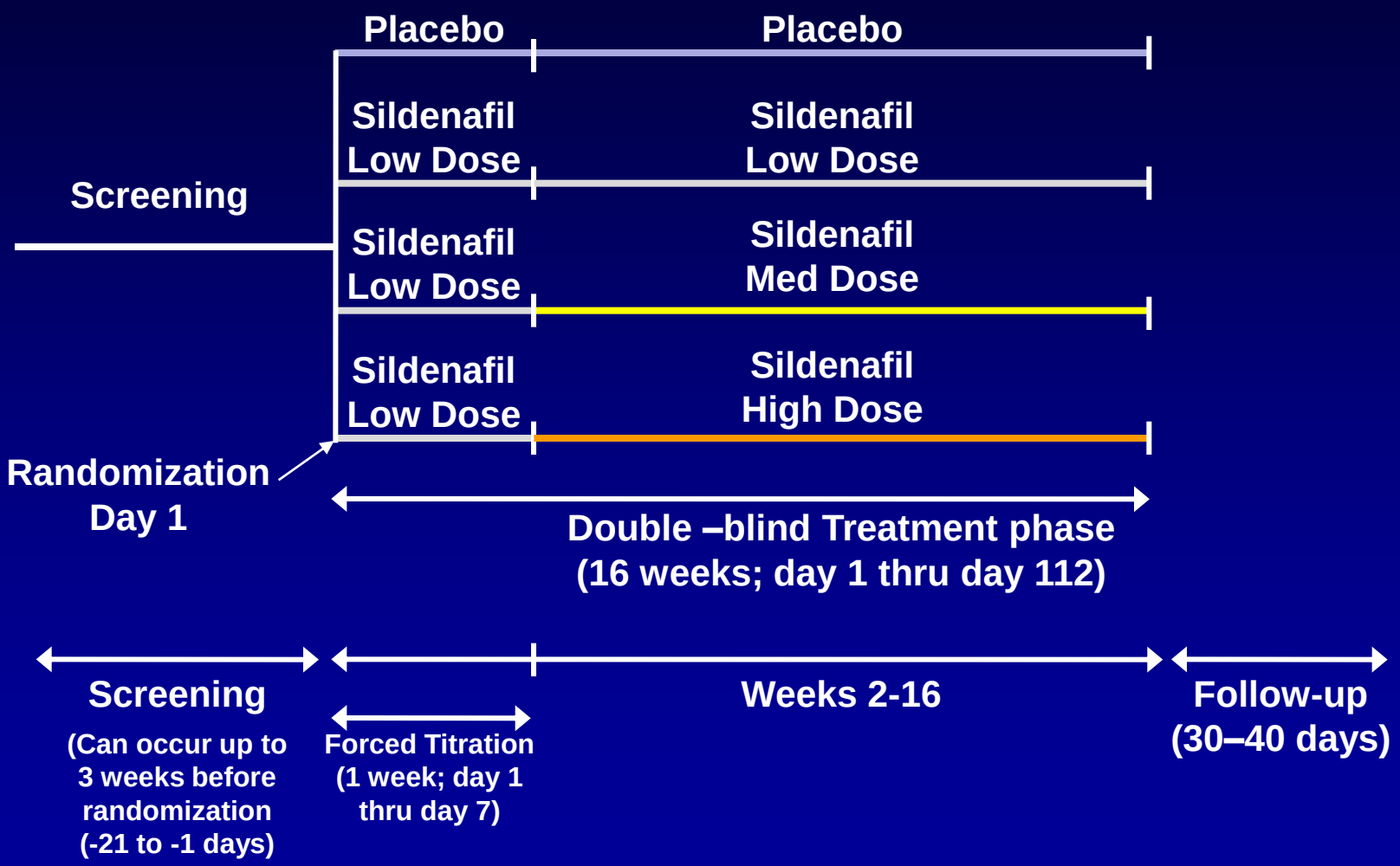
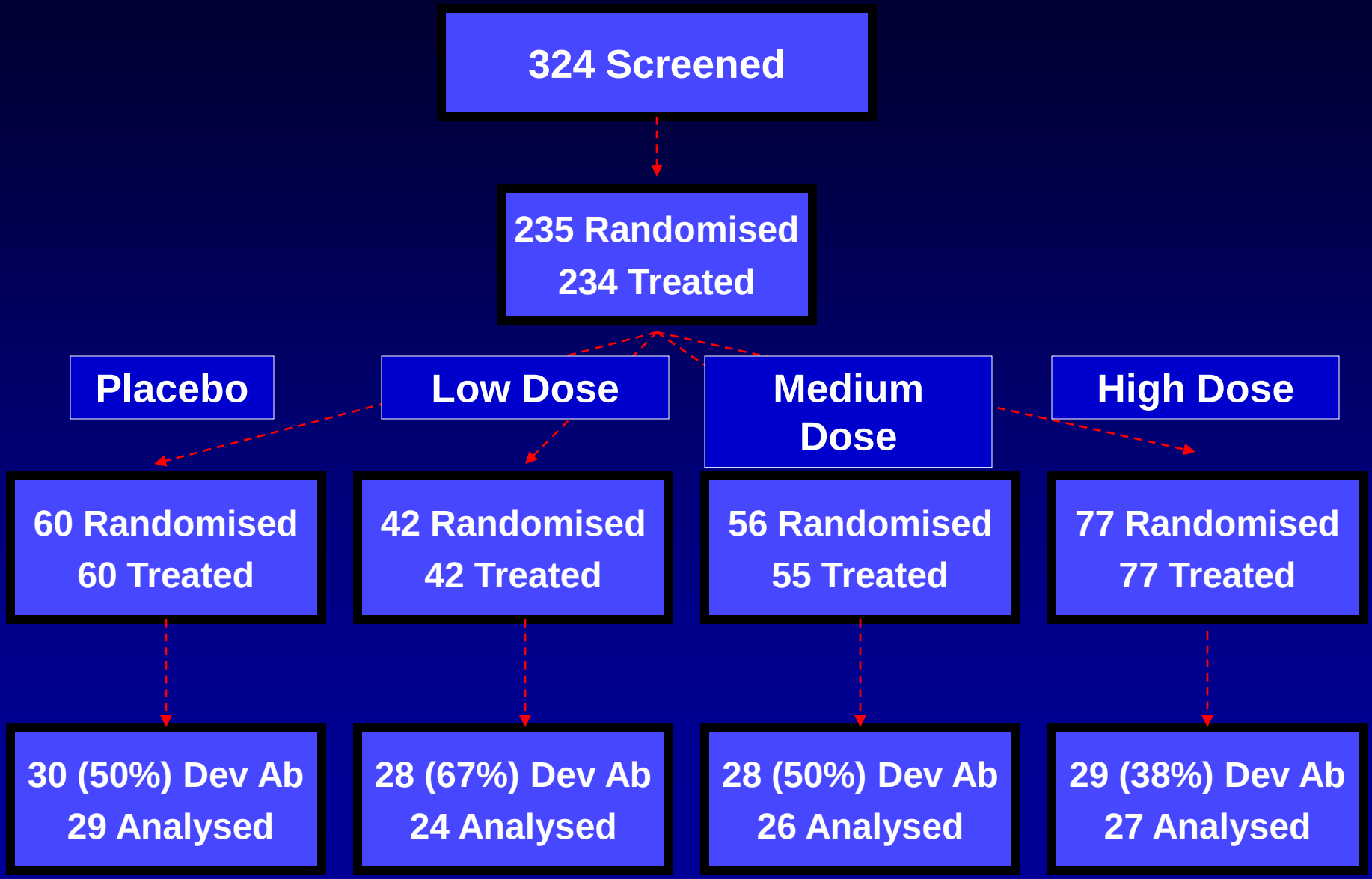
STARTS-1 Sildenafil Study Design



STARTS-1 Subject Accountability



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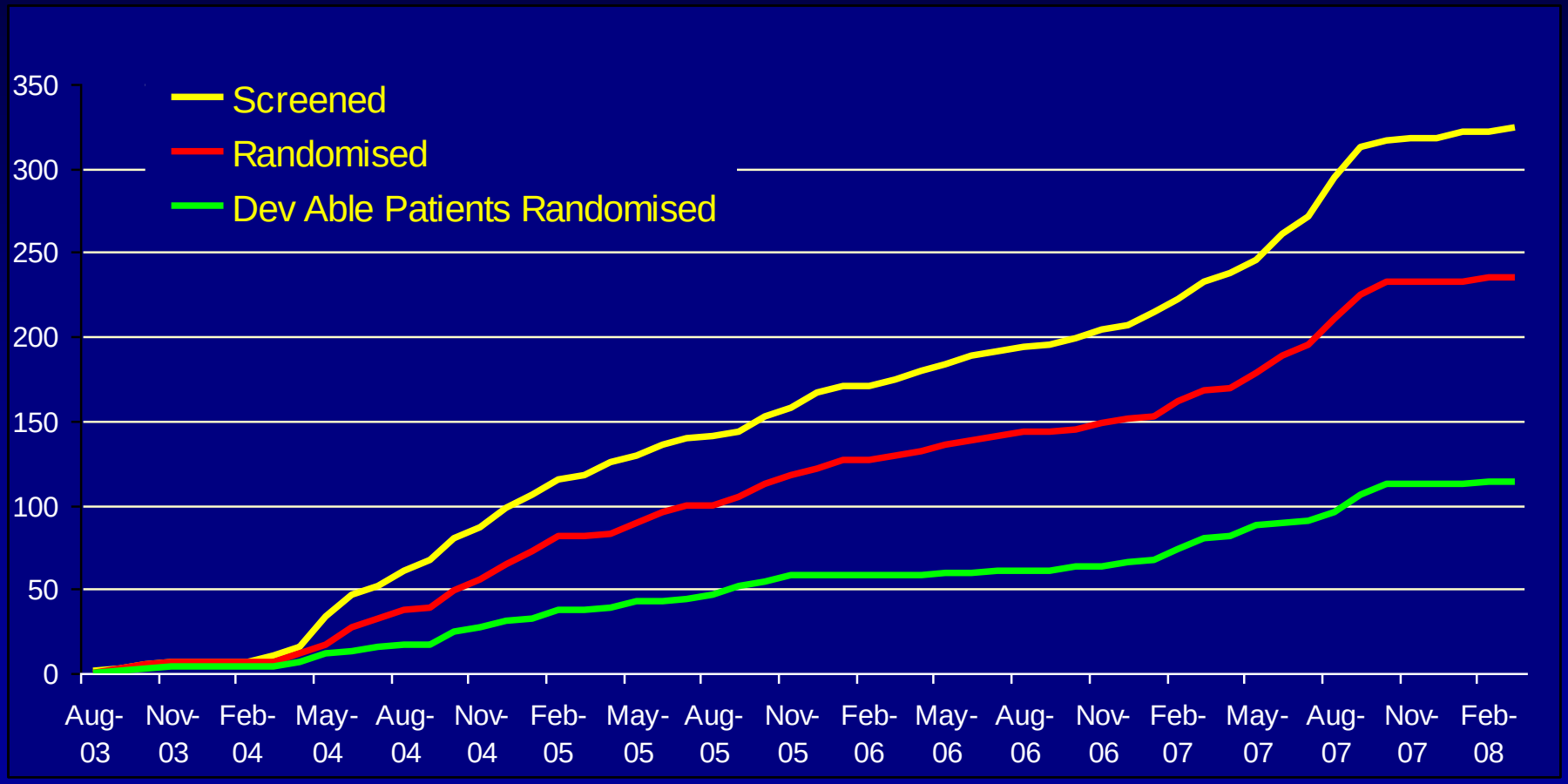
Time to Recruit 115 Subjects Capable of Reliable Exercise Capacity Testing



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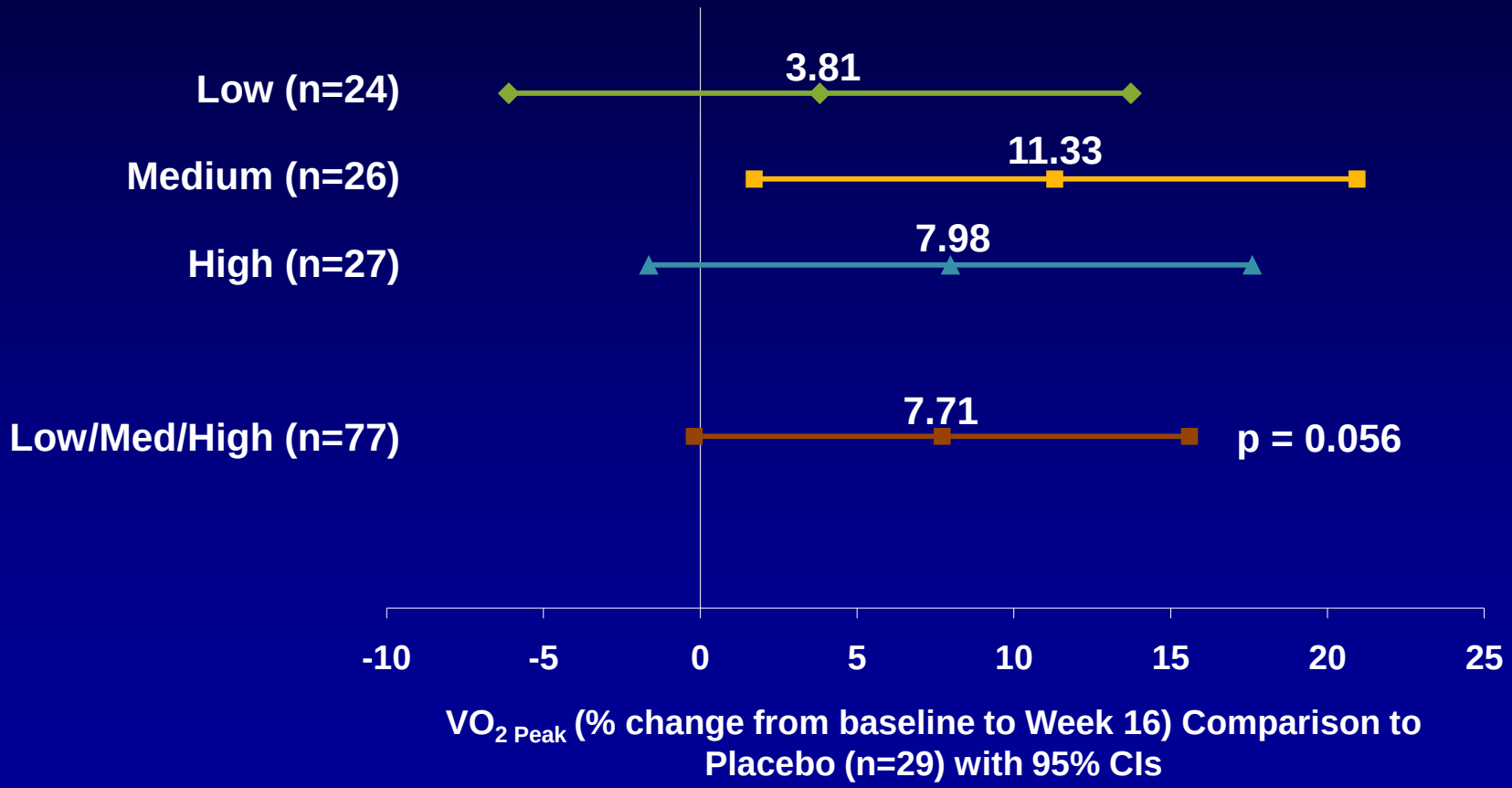
Disease Etiology

Primary Diagnosis	Placebo	Sildenafil
All subjects (N=234)		
IPAH	35%	33%
APAH-CHD	65%	67%
Developmentally able subjects (N=115)		
IPAH	33%	36%
APAH-CHD	67%	64%

Baseline $VO_{2\ Peak}$ & Hemodynamics

Mean (SD)	Normal Values	Placebo	Sildenafil Low/Medium/High (Combined)
$V0_{2\ Peak}$, ml/kg/min	30 – 35	20 (4) n=30	18 (4) n=85
mPAP, mmHg	12 – 15	59 (22) n=59	63 (22) n=172
CI, L/min/m^2	2.5 – 4	4 (2) n=59	3 (2) n=167
PVRI, dyne.sec.cm^{-5}.m^2	<160	1167 (759) n=57	1590 (1175) n=165

Placebo-adjusted Percent Change $VO_{2\ Peak}$



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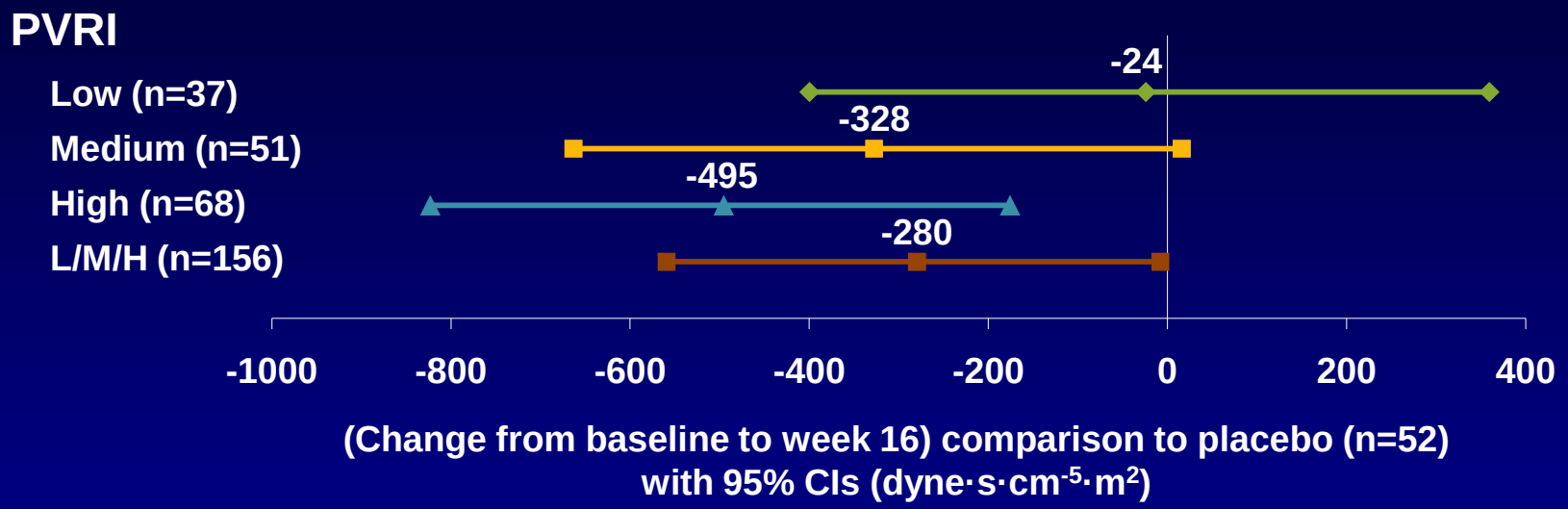
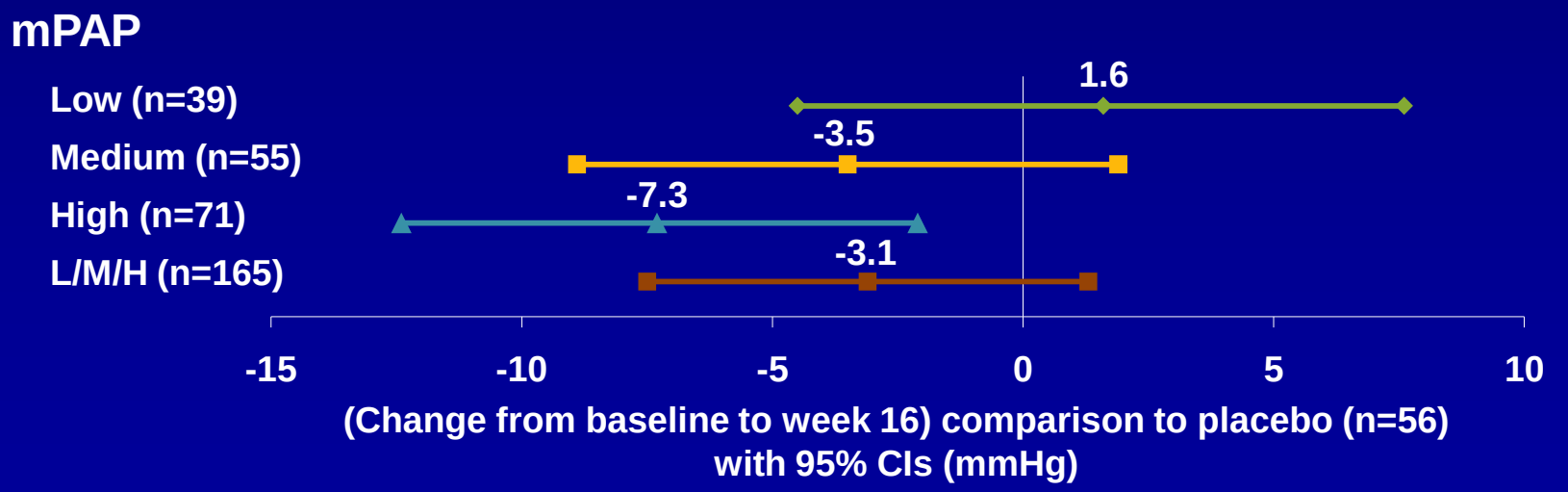
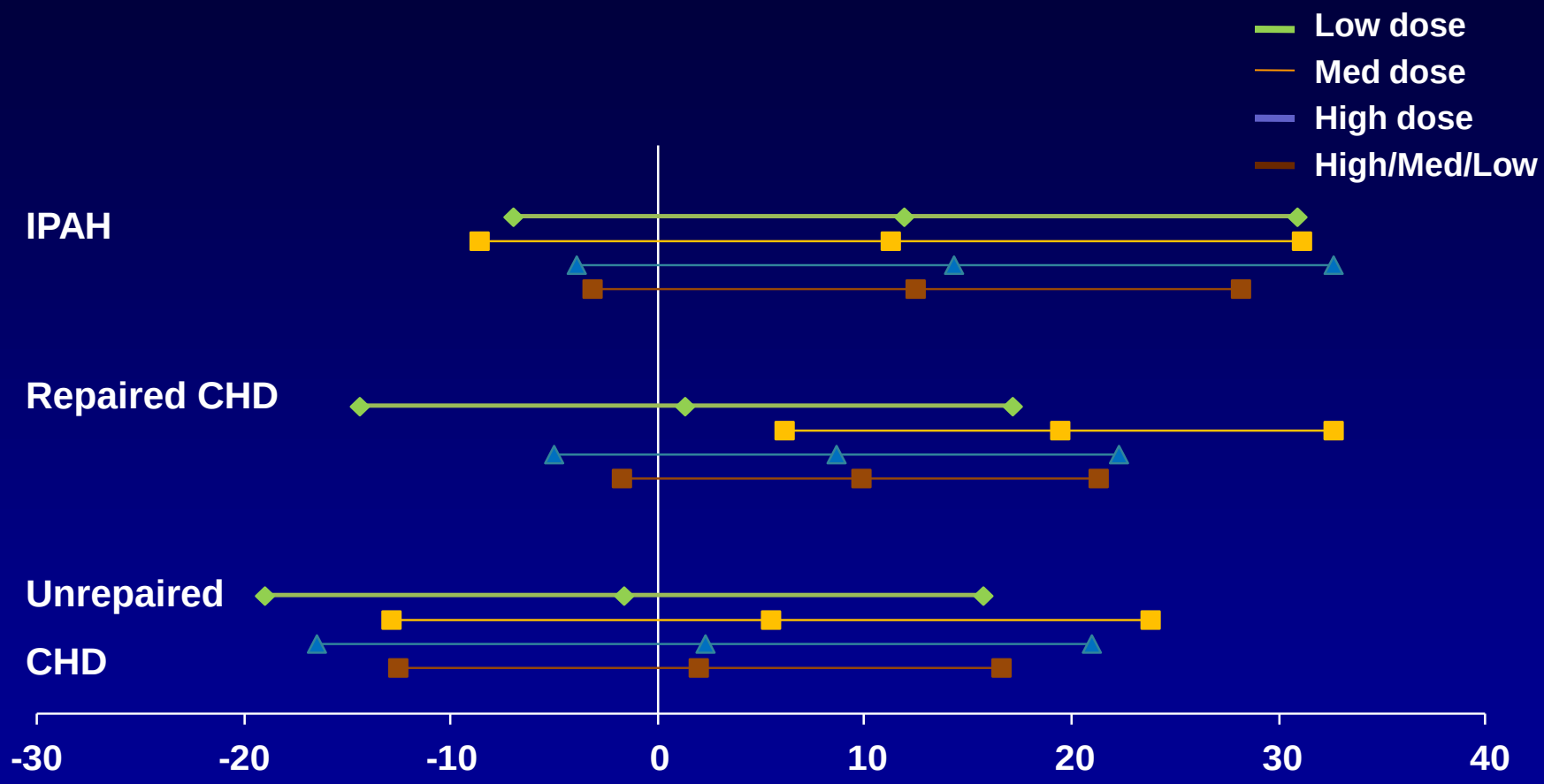
Effects of Sildenafil on PVRI and mPAP in Children



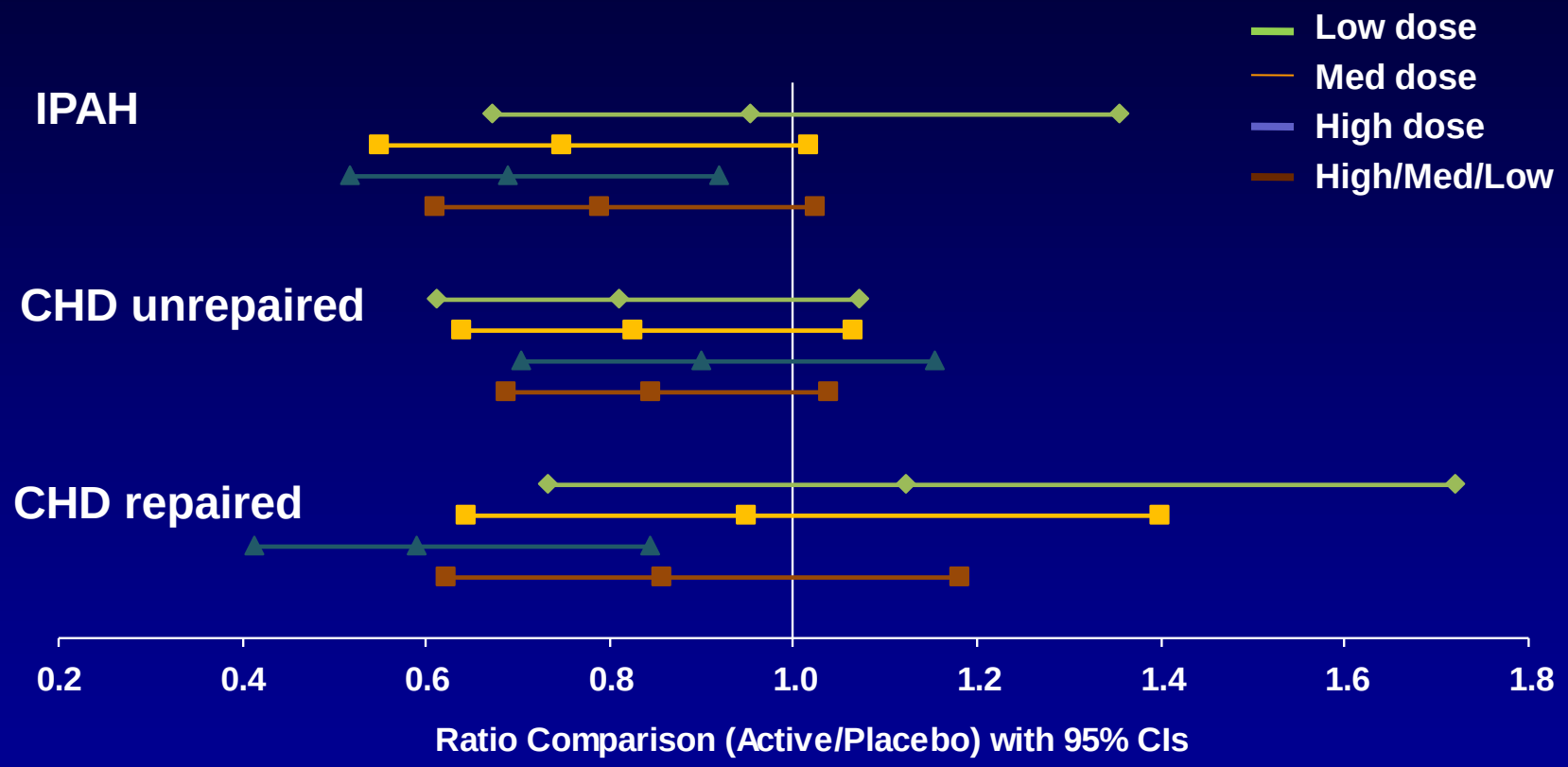


% Change in $VO_{2\ Peak}$ by Etiology



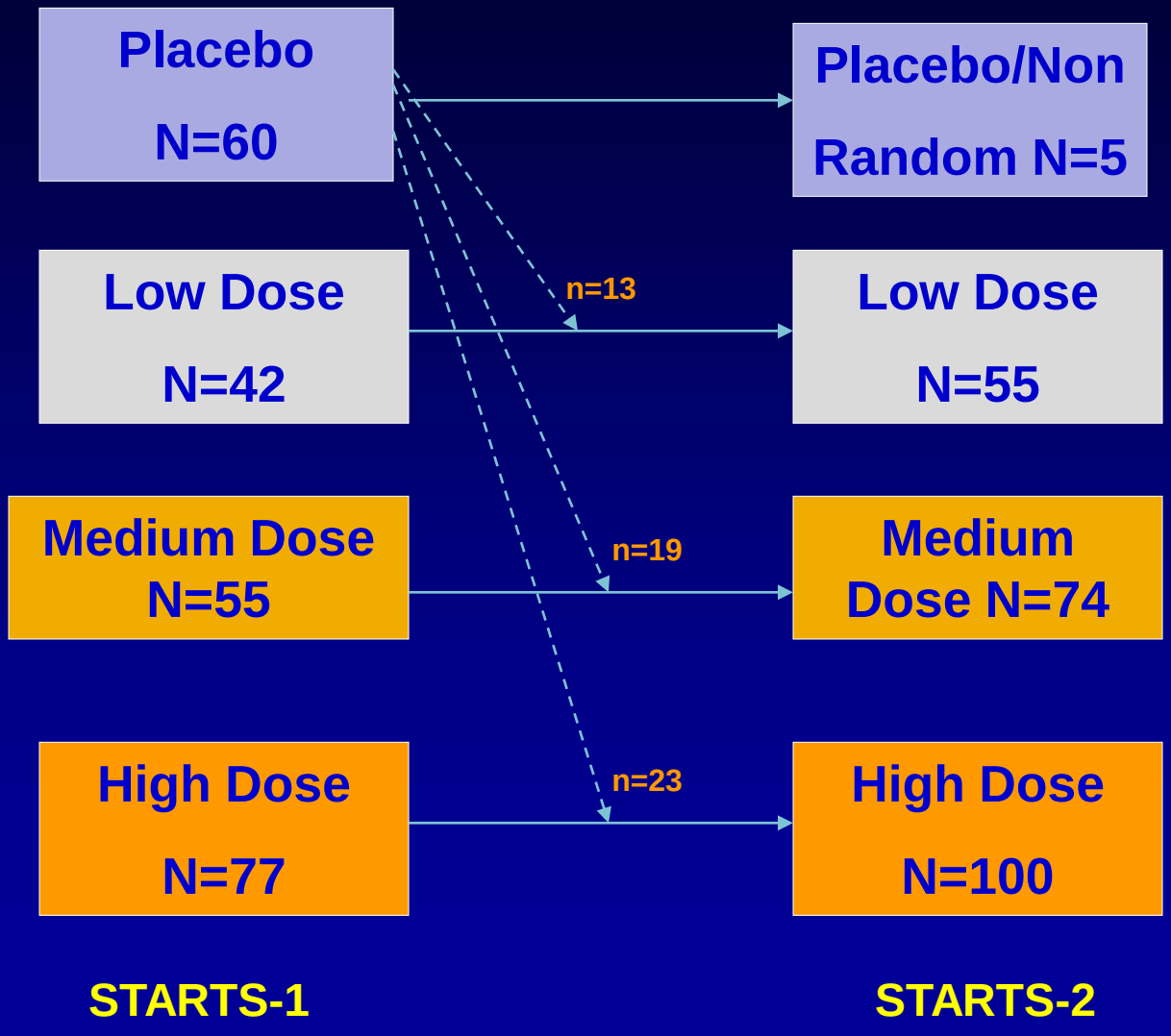
$VO_{2\ Peak}$ %Change from Baseline to Week 16 Comparison to Placebo with 95%CI

PVRI: Analysis by Etiology



Low dose Medium dose High dose Combined dose

Patient Disposition in STARTS-1 and -2



Sildenafil Dose Changes

Table 1. Summary of Dose Changes

	Sildenafil Dose		
	Low (n=55)	**Medium (n=74)**	**High (n=100)**
Down titrations, n (%)[‡]	0	2* (3)	4 (4)
At least 1 uptitration, n (%)	28 (51)	11 (15)	13 (13)[†]
1 uptitration	20 (36)	8 (11)	8 (8)[†]
2 uptitrations	8 (15)	3 (4)[†]	5 (5)[†]
Dose increases due to weight increases[§]	18 (33)	36 (49)	39 (39)

A maximum of 2 uptitrations and 1 downtitration were allowed during the study. Doses received after dose titrations were equivalent to those in other dose groups (see Methods).
*An additional 2 downtitrations occurred in patients who were treated with placebo in STARTS-1 but not randomized in STARTS-2.

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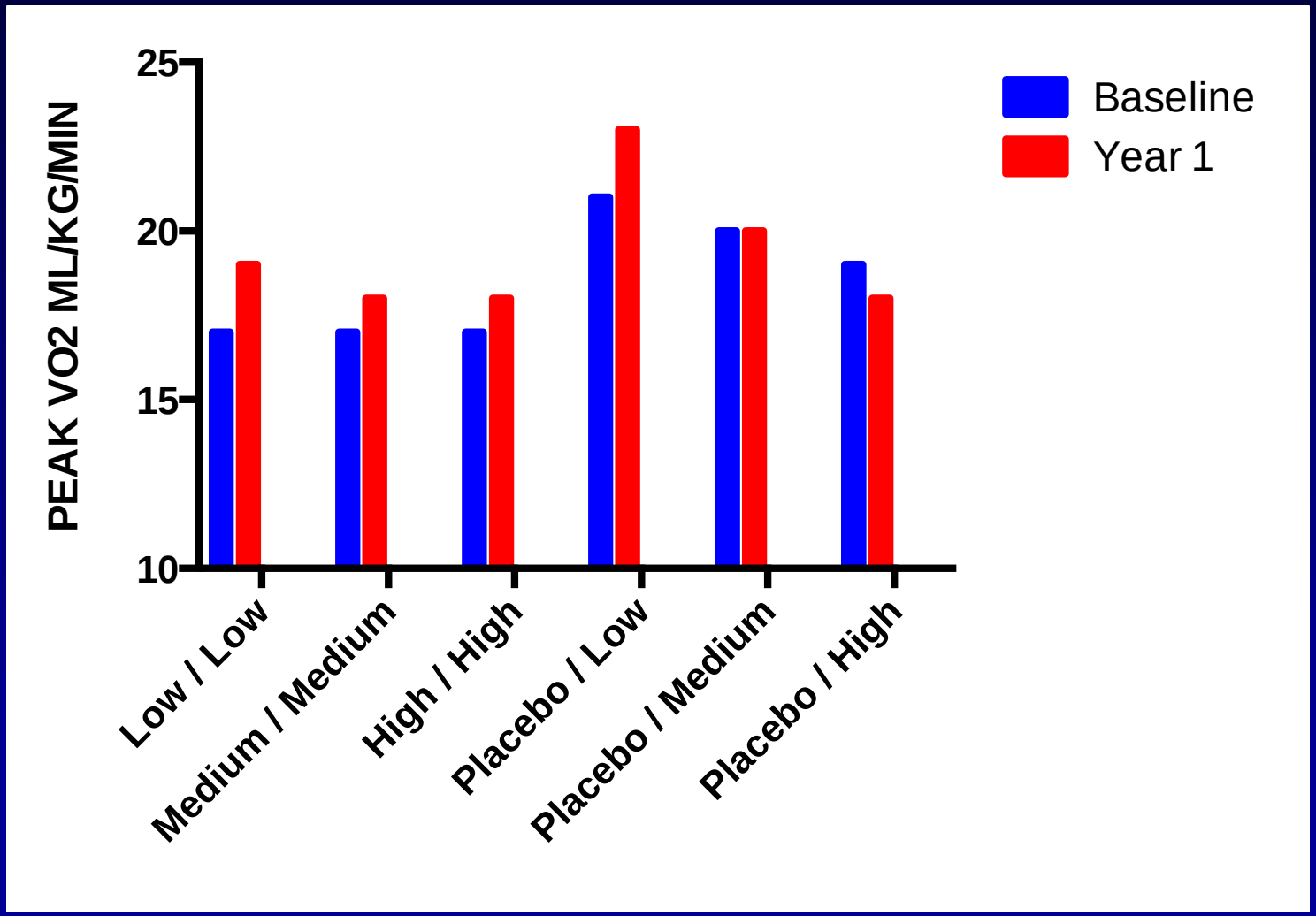
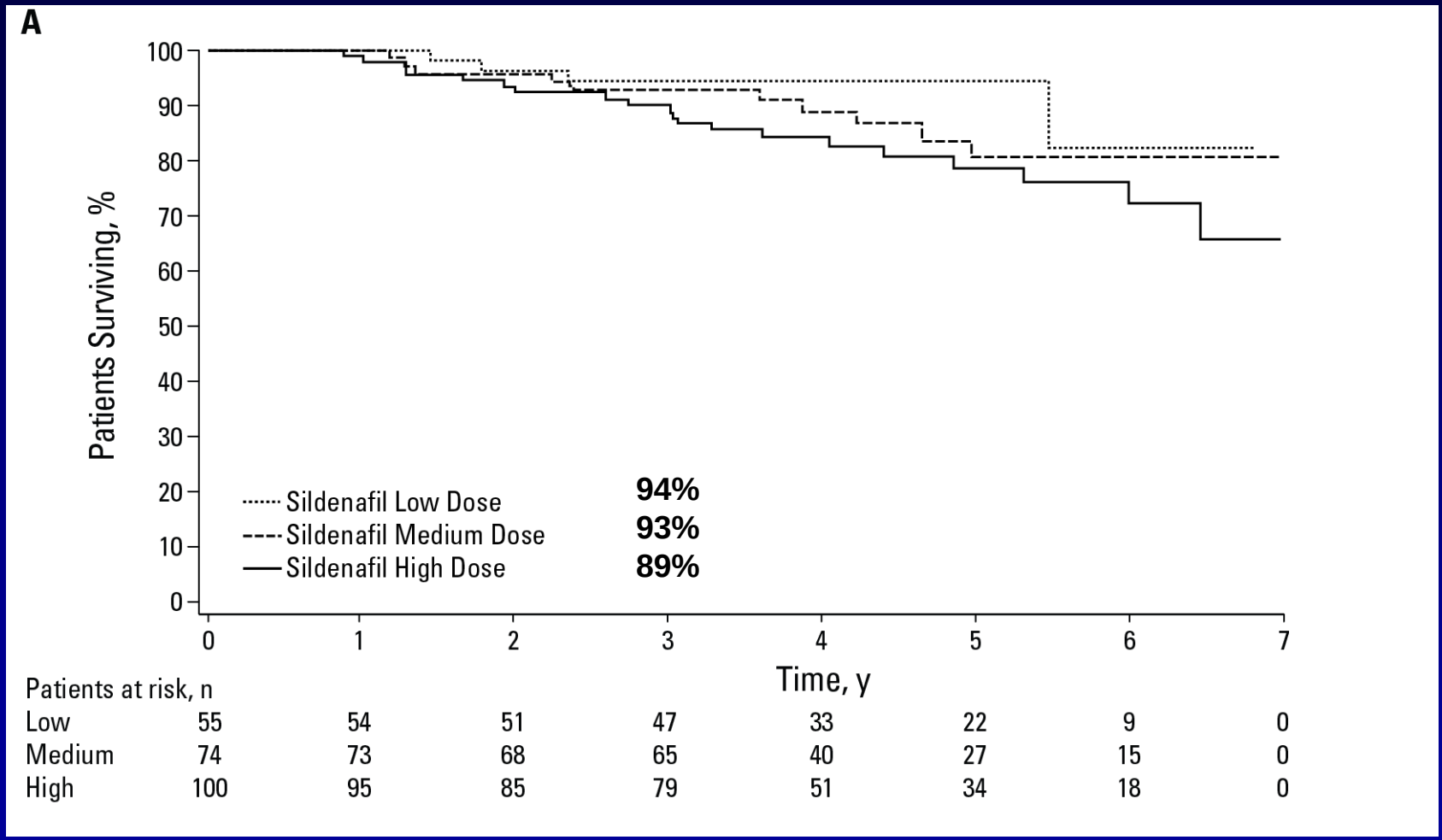
STARTS-2: 1 Year $VO_{2\ Peak}$

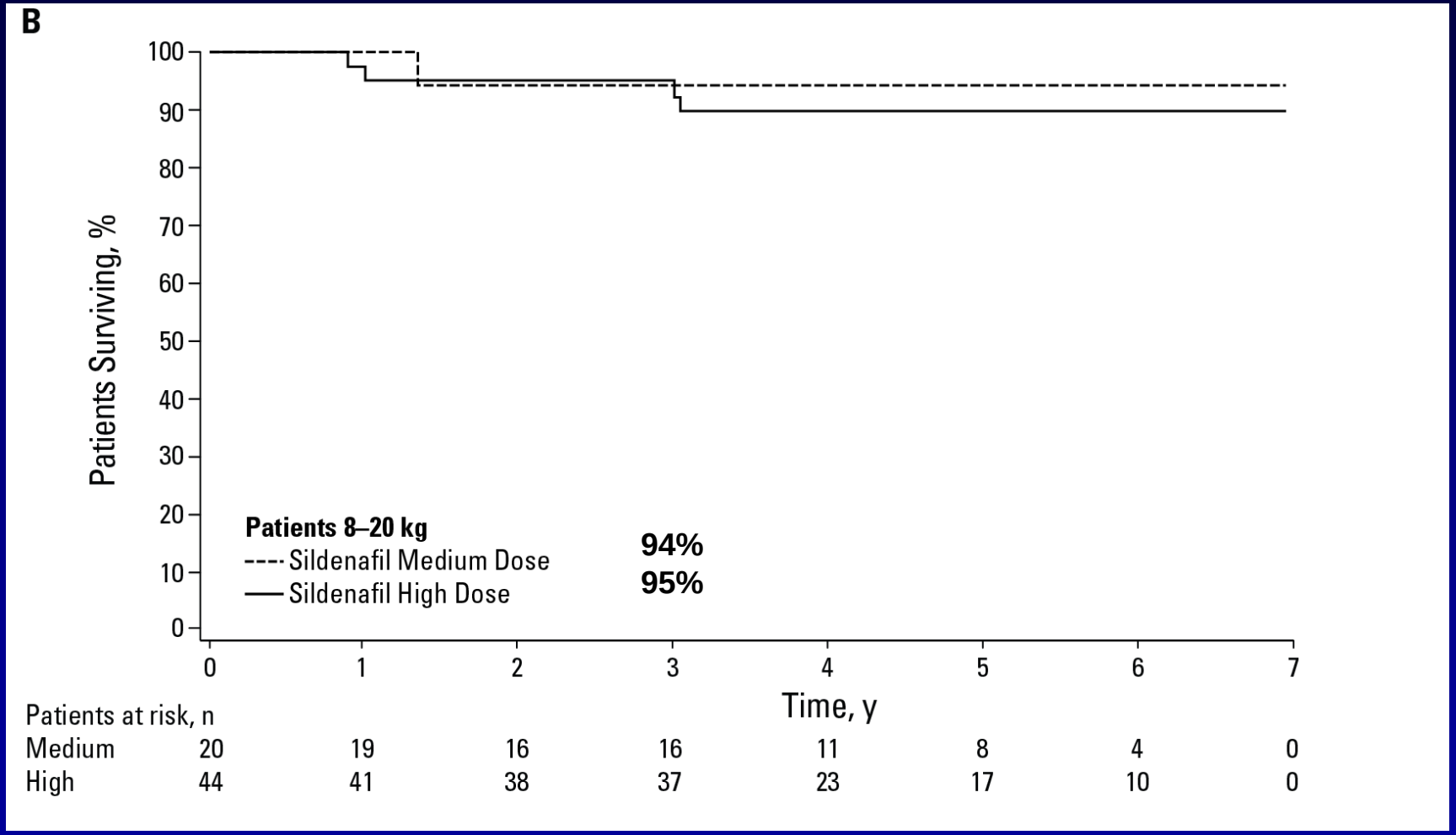


Kaplan-Meier Estimated Survival From Start of Sildenafil Treatment in STARTS-1 and -2



Hazard ratios for mortality were 3.50 (95% CI, 1.29–9.51) H vs L

Kaplan-Meier Estimated Survival From Start of Sildenafil Treatment in STARTS-1 and -2



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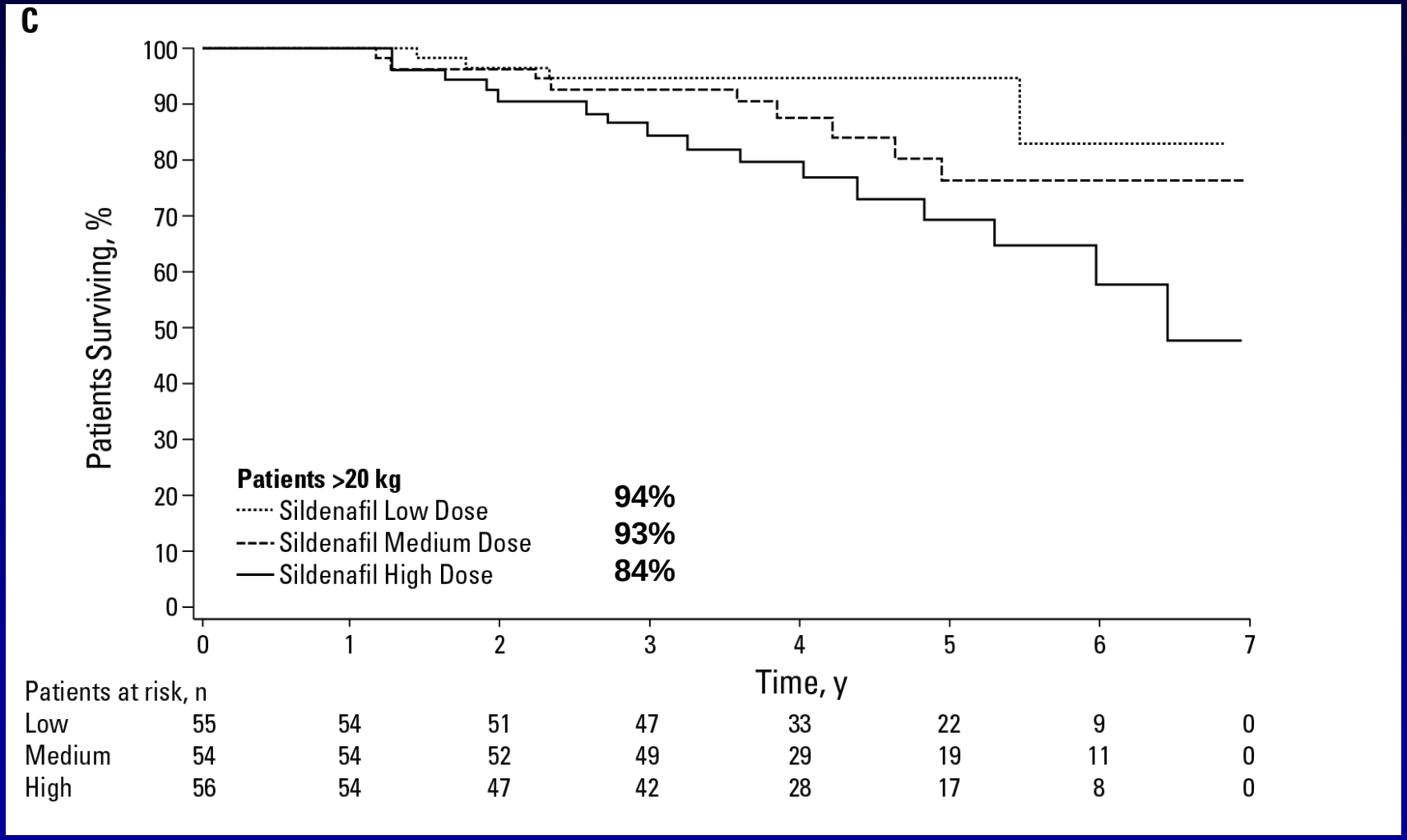
Kaplan-Meier Estimated Survival From Start of Sildenafil Treatment in STARTS-1 and -2



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Baseline Characteristics and Mortality

- 74% (26/35) of deaths were in IPAH children
- 74% (26/35) of the subjects who died had baseline PVRI ≥ to the median (15 Wood units□m2)
- 69% (24/35) had mPAP ≥ to the median (62 mmHg)
- 71% (25/35) had RAP to the median (7.0 mmHg)

Baseline Characteristics and Mortality

- 40% (14/35) were FC III/IV at baseline
- All deaths judged by investigator as disease related

Regulatory / DMC Actions

- May 2011: EMA approves sildenafil for pediatric use in children with PAH
- August 2011: STARTS DMC mandates decrease in sildenafil dose
- October 2011: EMA warns against use of high dose
- August 2012: FDA warns against use of sildenafil 1-17 y.o.
  - *high dose of Revatio had a higher risk of death than children taking a lower dose*
  - *low doses of Revatio are not effective in improving exercise ability in the 16 week randomized placebo controlled* trial

Study Limitations

- No control group in LT extension
- 26% (9/35) of patients who died withdrew from STARTS-1/-2 study and f/u treatment unknown
  - No treatment protocol after withdrawal
  - Death median of 147 days (9-406 days) after off study treatment

Conclusions

- Primary endpoint of STARTS-1 did not meet predefined statistical p value – peak VO2 for all sildenafil treated patients vs PBO
- Dose-related increase in mortality observed at 3 years
- Survival in treatment naïve children 88-94% at 3 years on L/M/H dose sildenafil monotherapy
- Survival in STARTS similar to 3 year survival in 3 recent registries (UK, Netherlands, US)