Efficacy of Tirilazad Mesylate in Aneurysmal Sub-Arachnoid Hemorrhage

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Peripheral and Central Nervous System Drugs Advisory Committee Meeting

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Background

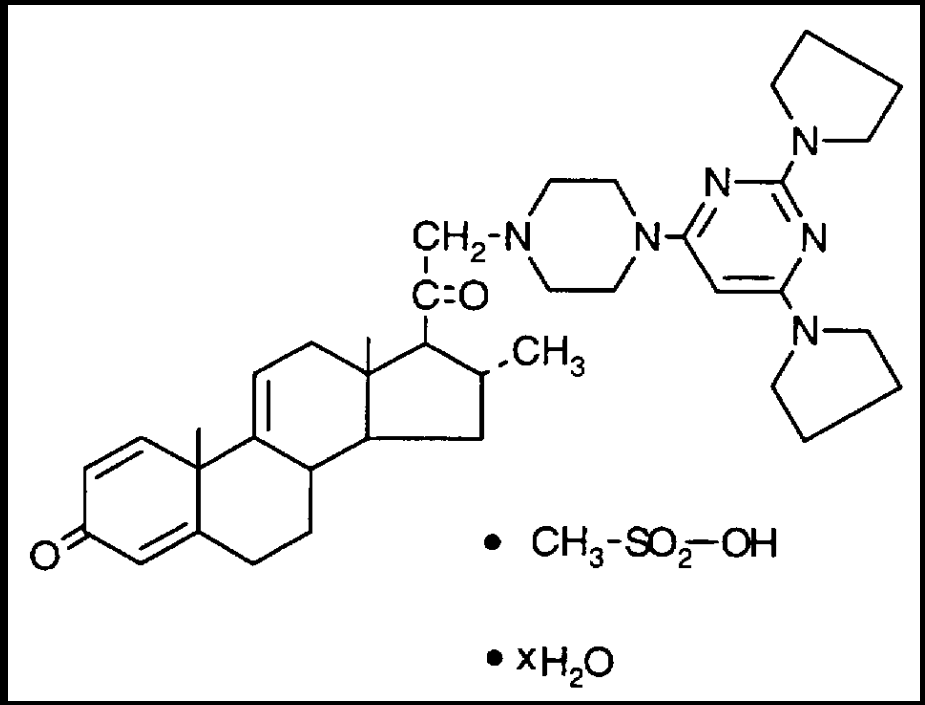
Efficacy

Discussion

Proposed Indication

… for the treatment of aneurysmal subarachnoid hemorrhage (SAH) to improve survival and functional outcome in patients with poor neurologic function following the initial hemorrhage. Treatment should be initiated within the first 48 hours.

Tirilazad mesylate



- $T_{1/2}$ 61-123 hrs
- hepatic excretion
- ↑ clearance in Females

NDA 20-399

- 6/10/94 - NDA submitted
- 2 large multicenter efficacy studies (32 / 29)
- 9/26/94 - PCNS Committee meeting
- 6/5/95 - non-approvable letter: evidence of efficacy in men; need to demonstrate efficacy in women
- Studies 65 / 63 conducted in women

Background

Efficacy

Discussion

Efficacy in SAH

Original NDA 20-399
6/10/94

Study 32

Study 29

Supplemental NDA
7/24/98

Study 65

Study 63

Efficacy Studies

- Similar design
- Randomized, double-blind, vehicle-controlled, multicenter
- Aneurysmal SAH ≤ 48 hours
- All neurogrades
- Concomitant nimodipine

Efficacy Studies
Treatment Regimen

- Intravenous, divided doses every 6 hours
- treatment continued until day 10
- 8-10 days of dosing (32-40 doses), depending when medication started

Neurograde

- Proposed treatment population is SAH patients with poor neurologic function following the initial hemorrhage
- poor neurologic function was defined using the Neurograde

Glasgow Coma Scale (GCS)

Component	Level of Response
Eye Opening	1 = no response 2 = to pain 3 = to voice 4 = spontaneously
Verbal	1 = no response 2 = incomprehensible words 3 = inappropriate words 4 = disoriented 5 = oriented
Motor Response	1 = no response 2 = abnormal extension (decerebrate) 3 = abnormal flexion (decorticate) 4 = withdrawal 5 = localizes 6 = follows commands

Modified GCS (mGCS)

- eye opening
- verbal
- 4 individual limb motor responses

mGCS = eye + verbal + *WORST* motor

Missing mGCS Components

- Imputation Algorithm for missing component scores
- Verbal Score most likely to be missing (intubation)

Variable	mGCS
All three components missing	No imputation is done, score is “missing”
All three components other or untestable	Each component imputed = 1, Total score = 3
All 4 limb component scores missing	Motor score imputed = 1
Eye opening component score missing	Eye score imputed = 1
Verbal component score missing	Verbal score imputed = 1
Eye opening other/untestable/unknown	Eye score imputed = 1
Verbal other/untestable/unknown	Verbal score imputed = 1
Verbal intubated/tracheostomy	Verbal score imputed = 1

Neurograde

	Grade	mGCS
Low	I	15
	II	13-14
	III	9-12
High	IV	6-8
	V	3-5

Neurograde vs. Hunt & Hess Scale

- H&H used in the nimodipine trials

Grade	mGCS
I	15
II	13-14
III	9-12
IV	6-8
V	3-5

Grade	Hunt & Hess
I	No neurological deficit
II	Meningismus only
III	Drowsiness or a Neurological deficit
IV	Severe neurological Deficit
V	Moribund

Efficacy Endpoints

Mortality at 3 months

Glasgow Outcome Scale (GOS) at 3 months

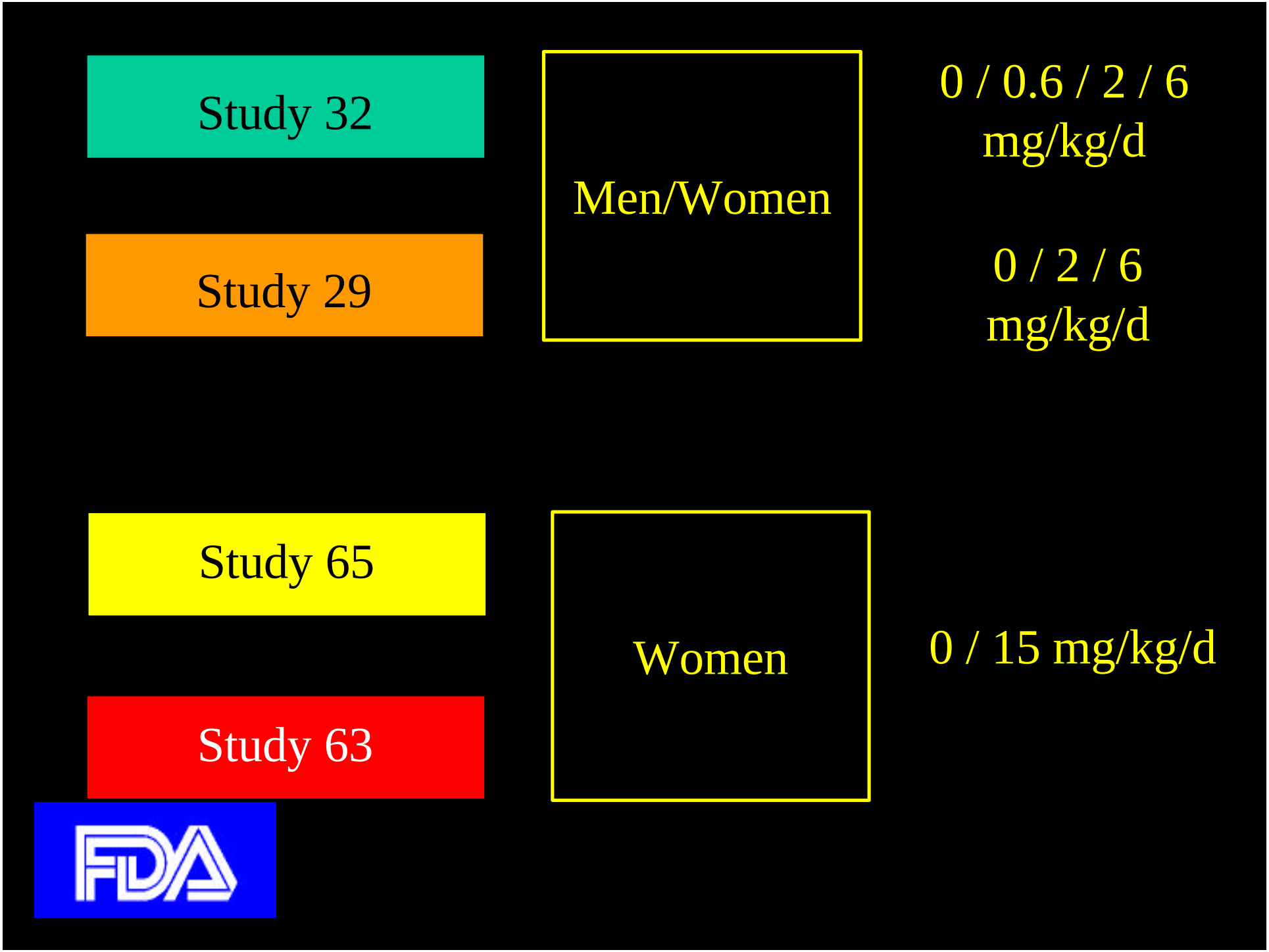
Clinical Vasospasm

Glasgow Outcome Scale (GOS)

Outcome	GOS
Good recovery	1
Moderate disability	2
Severe disability	3
Vegetative survival	4
Death	5

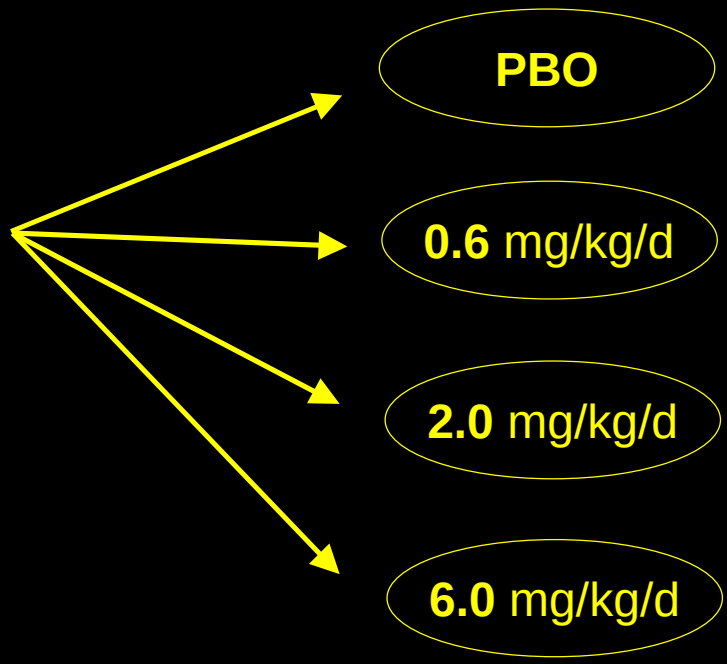
Other Efficacy Endpoints

- Need for HHH therapy
- neurologic worsening from vasospasm
- cerebral infarction during treatment


Study 32
Study 29
Men/Women
0 / 0.6 / 2 / 6 mg/kg/d
0 / 2 / 6 mg/kg/d
Study 65
Study 63
Women
0 / 15 mg/kg/d
FDA

Study 32

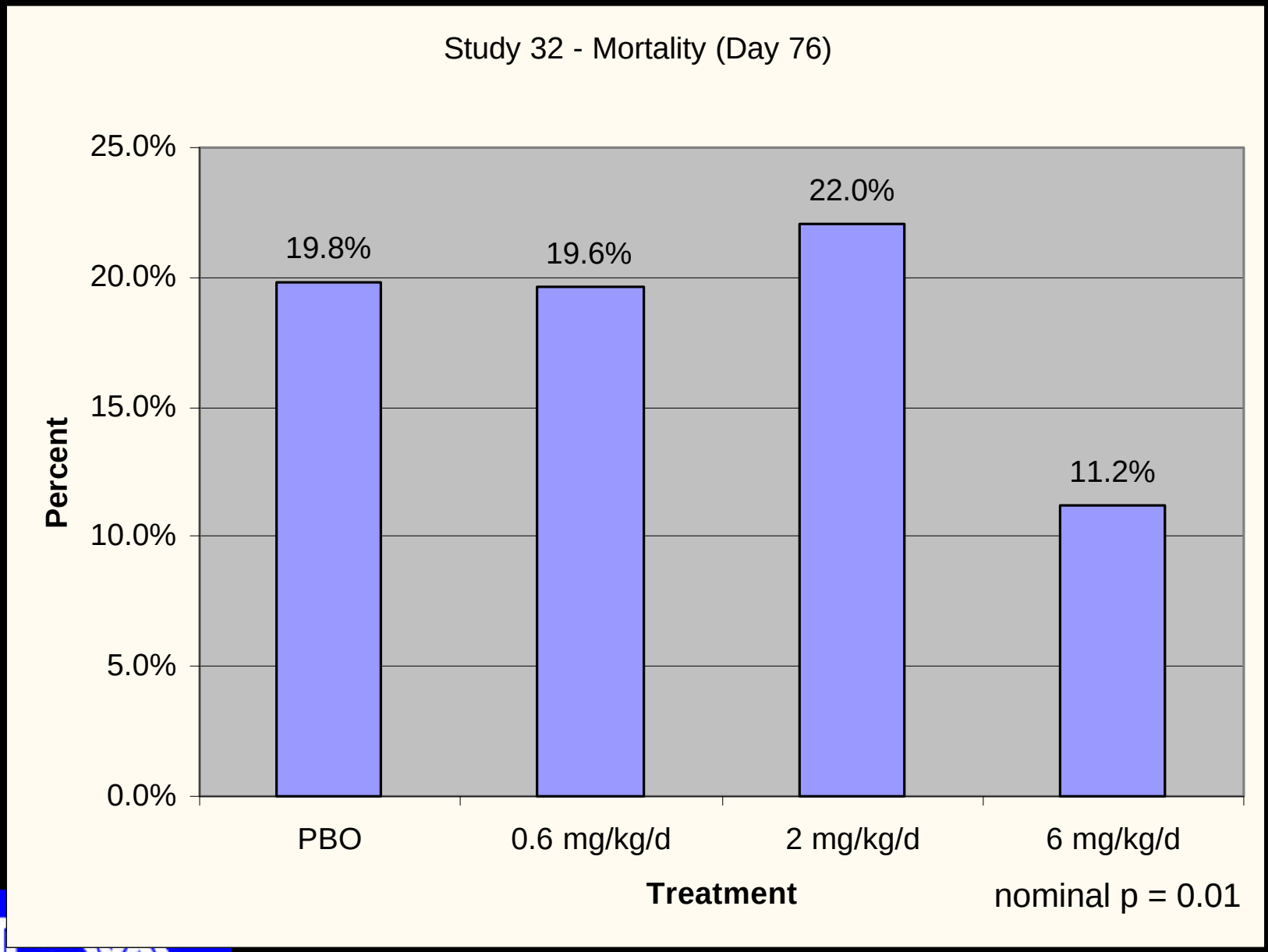
- 12/91 - 8/93 in Europe, Australia, NZ
- Men/Women
- N=1,015
- 4 Treatment Groups
- + Nimodipine



PBO = vehicle placebo

Study 32 - Primary Efficacy Endpoint

Vasospasm



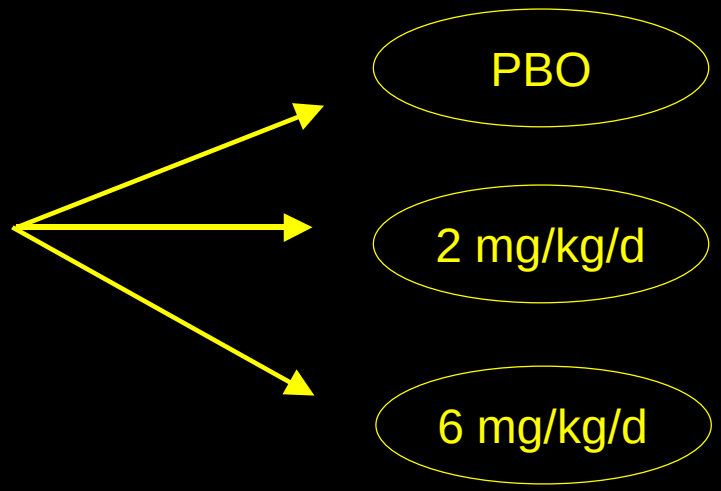
PBO = vehicle placebo

Study 32 - Mortality by Sex

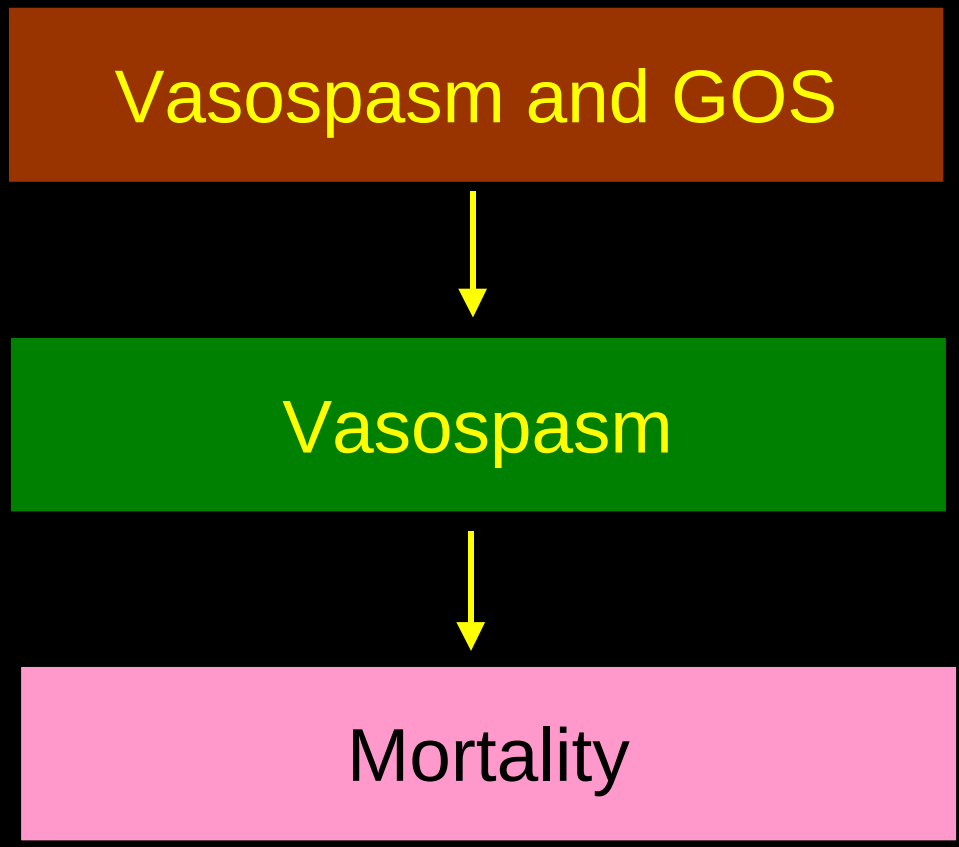
Group	PBO	6 mg/kg/d	nominal p value
Day 76			
All	49/247 (19.8%)	28/249 (11.2%)	0.010
Males	20/79 (25.3%)	2/97 (2%)	<0.001
Females	29/168 (17.3%)	26/152 (17.1%)	

Study 29

- 6/92 - 5/94 in U.S. and Canada
- Men/Women
- N=897
- 3 Treatment Groups
- + Nimodipine



Study 29 - Primary Efficacy Endpoint



Study 29 - Mortality

Group	Placebo	6 mg/kg/d	nominal p value
Day 76			
All	46/293 (15.7%)	37/288 (12.8%)	0.349
Males	10/78 (12.8%)	9/104 (8.7%)	0.444
Females	36/215 (16.7%)	28/184 (15.2%)	NS

NS = not significant

Study 29 - Mortality in High Neurogrades

Group	Placebo	6 mg/kg/d	nominal p value	adjusted p value*
Day 76 (sponsor)				
IV/V Males	4/12 (33.3%)	1/20 (5%)	0.033	
IV/V Females	16/42 (38.1%)	14/41 (34.1%)	NS	
Day 91 (FDA)				
IV/V Males	4/12 (33.3%)	2/20 (10%)	0.0758	0.6064
IV/V Females	16/42 (38.1%)	14/43 (32.6%)	NS	

* adjusted for: 2 doses, 2 genders, 2 NG subgroups

Non-approvable Letter (6/95)

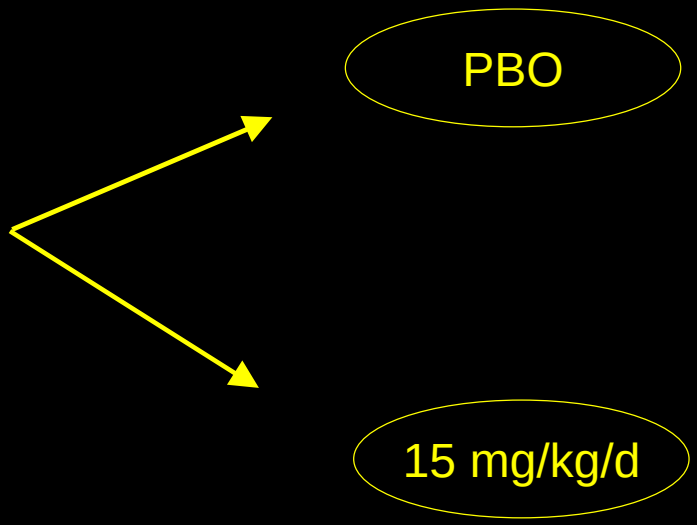
- Study 32, high-dose, men: positive mortality effect statistically robust
- Study 29: finding not reproduced
- Insufficient evidence of efficacy
- Still needed: evidence for reduced mortality and improved functional outcome in women

Response to NA letter

- 7/24/98 - response to non-approvable letter
- 2 large multicenter efficacy studies in women (65 / 63)
- higher dose (15 mg/kg/d)

Study 65

- 11/94 - 6/96 in Europe, Australia, NZ
- Women
- N=817
- 2 Treatment Groups
- + Nimodipine



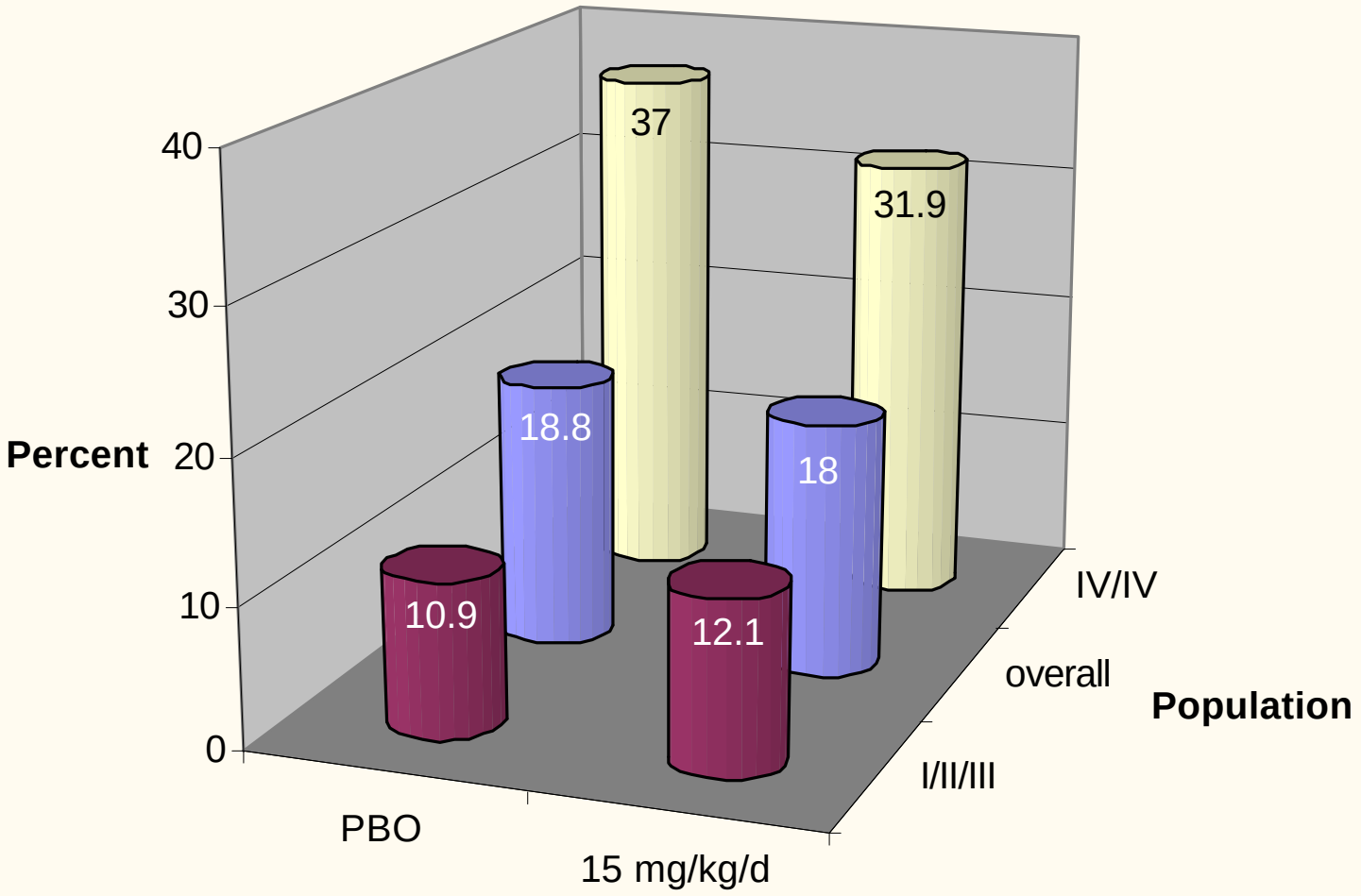
Study 65 - Mortality

- Primary Endpoint: Mortality at day 91
- Retrospective Analysis: low vs. high NG
- No treatment effect on mortality

Population	No. of Patients*		No. of Deaths (n, %)		p-value
	PBO	TIR	PBO	TIR	
Overall	394	389	74 (18.8)	70 (18.0)	0.776
Neurograde I/II/III	275	273	30 (10.9)	33 (12.1)	0.665#
Neurograde IV/V	119	116	44 (37.0)	37 (31.9)	0.413#

* Total number of patients known to be dead or alive at day 91
\# nominal p-value

Study 65 - Mortality (Day 91)



Study 65 - Other Endpoints

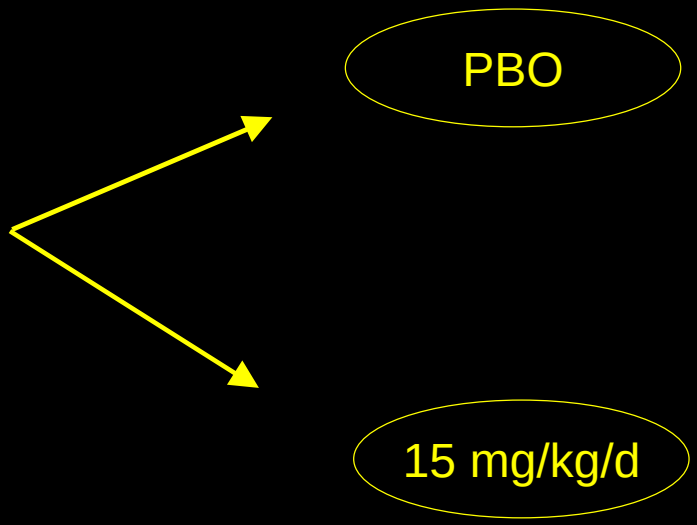
- Nominally Significant
  - Clinical vasospasm
  - Death from Clinical Vasospasm
- Negative
  - 3-month GOS
  - HHH Therapy
  - Neuroworsening
  - Cerebral Infarction
  - Angioplasty

Study 65 - Conclusions

- No improvement in mortality in women
- No improvement in functional outcome
- Decreased incidence of clinical vasospasm without demonstrable improvement in other measures (mortality, functional outcome, cerebral infarction)

Study 63

- 3/95 - 2/97 in North America
- Women
- N=823
- 2 Treatment Groups
- + Nimodipine



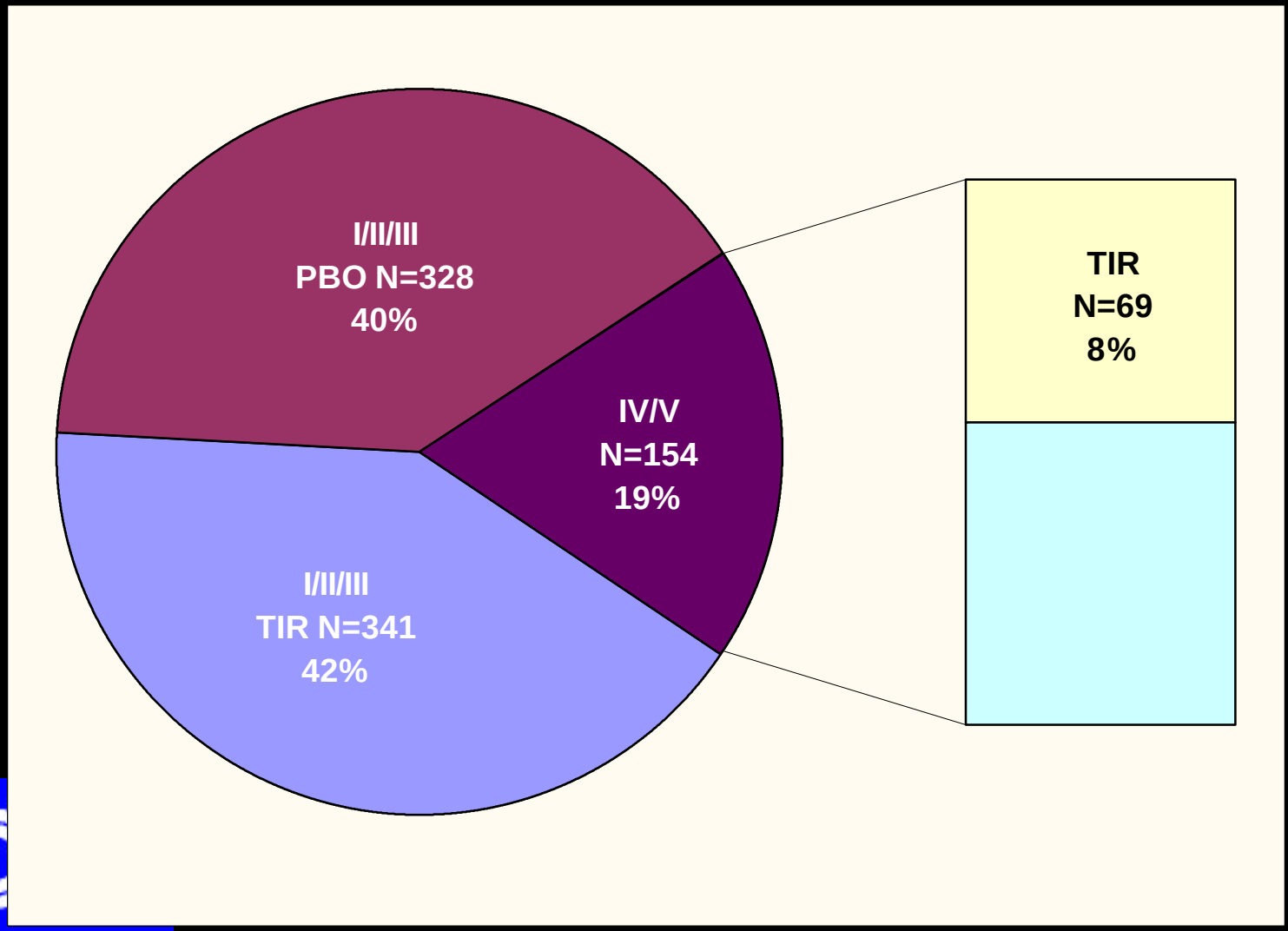
Study 63 - Primary Efficacy

- Original Primary Endpoint: Mortality
- Amendment 5 filed 12/16/96:

  Mortality in Neurograde IV/V

Study 63 - Exposures

(N=823; TIR=410, PBO=413)



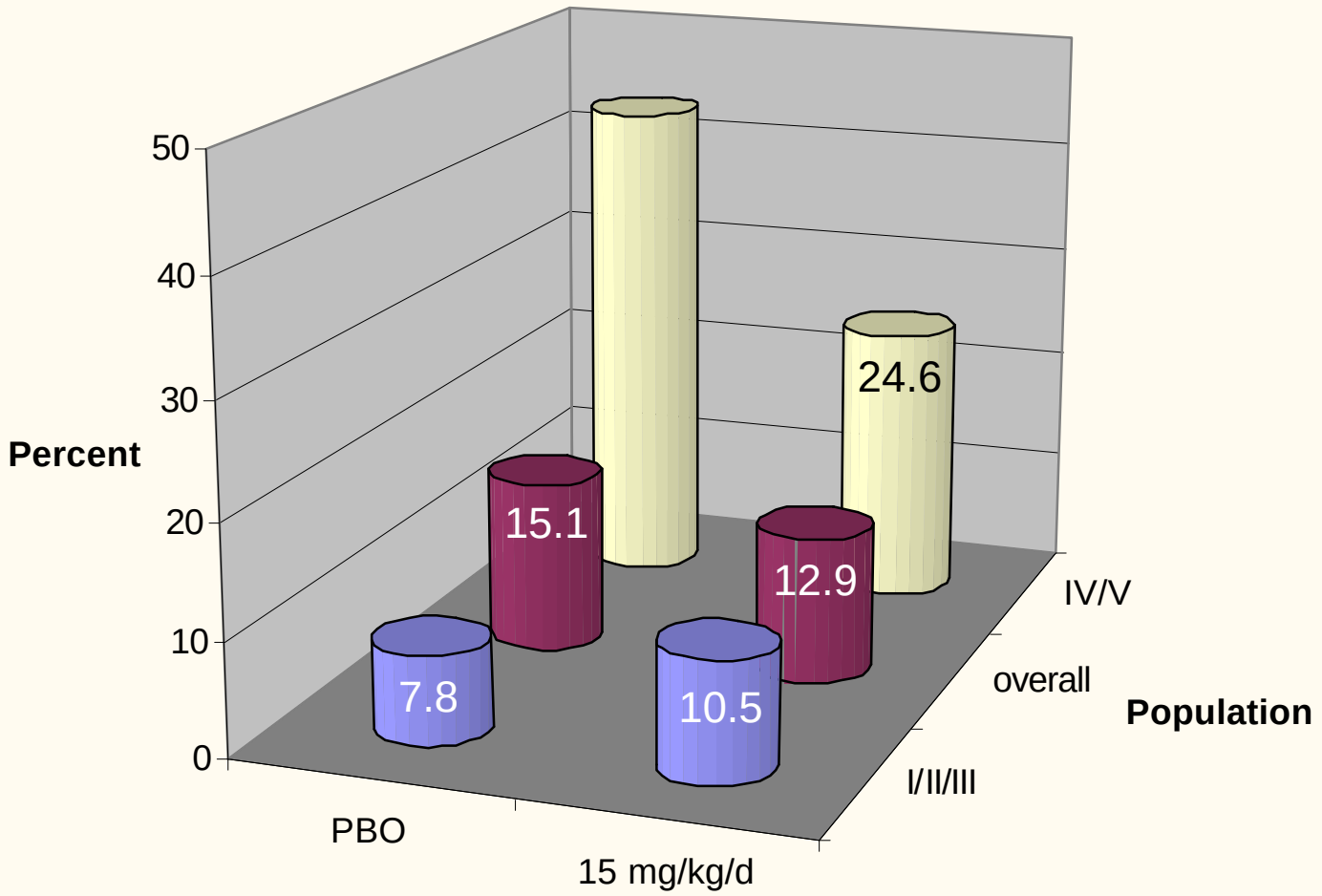
Study 63 - Mortality

- Primary Endpoint: Mortality at day 91 in high neurogrades (IV/V)
- Statistically significant reduction in mortality

Population	No. of Patients*		No. of Deaths (n, %)		p-value
	PBO	TIR	PBO	TIR	
Overall	404	403	61 (15.1)	52 (12.9)	0.369
Neurograde I/II/III	321	334	25 (7.8)	35 (10.5)	0.233
Neurograde IV/V	83	69	36 (43.4)	17 (24.6)	0.016

* Total number of patients known to be dead or alive at day 91

Study 63 - Mortality (Day 91)



3-month GOS Analysis

Outcome	GOS
Good recovery	1
Moderate disability	2
Severe disability	3
Vegetative survival	4
Death	5

- Three binary analyses of equal interest:
  - Good Recovery: GOS 1 vs. all others
  - Favorable Outcome: GOS 1, 2 vs. all others
  - Vegetative/Death: all others vs. GOS 4, 5

Study 63 - GOS (IV/V)

GOS Level	Odds Ratio*	95% CI	p-value
Composite	0.55	0.31-1.00	0.048
Good Recovery	0.52	0.24-1.11	0.089
Favorable Outcome	0.72	0.37-1.38	0.320
Vegetative/Death	0.47	0.24-0.94	0.034

* odds ratio < 1 favors drug

Study 63 - GOS (cont'd)

GOS Level	Odds Ratio*	95% CI	p-value
Overall – Treatment Comparison Adjusted for Neurograde			
Composite	0.87	0.62-1.21	0.401
Good Recovery	0.82	0.55-1.25	0.360
Favorable Outcome	1.04	0.71-1.53	0.834
Vegetative Death	0.78	0.51-1.20	0.262
Neurograde I-III – Treatment Comparison Unadjusted			
Composite	1.35	0.98-1.84	0.064
Good Recovery	1.32	0.95-1.82	0.095
Favorable Outcome	1.52	1.03-2.24	0.037
Vegetative Death	1.29	0.78-2.15	0.324

* odds ratio < 1 favors drug

Study 63 - Other Endpoints

- Negative
  - Clinical Vasospasm
  - HHH Therapy
  - Neuroworsening
  - Neuroworsening or death from Clinical Vasospasm
  - Cerebral Infarction
  - Angioplasty

Study 63 - Conclusions

Tirilazad therapy was associated with:

- Statistically significant decrease in mortality in high neurograde (drug effect?)
- Improvement in functional outcome in high neurograde (reflection of mortality analysis)
- Worsening of functional outcome + mortality numerically higher in low neurograde

Background

Efficacy

Discussion

Discussion
(Four Questions)

1. Is there substantial evidence of efficacy?

2. Can clinicians identify the target population easily and accurately?

3. Is there a risk to low neurograde patients?

4. What is the effect of concomitant nimodipine in high neurograde patients?

1. Evidence of Efficacy

- Study 32 negative on vasospasm
  - positive mortality effect in men
- Study 29 negative on mortality
  - positive numerical mortality effect on IV/V men
- need evidence in women
- Study 65 negative on mortality
  - positive numerical mortality effect on IV/V women
- Study 63 positive in IV/V women

Efficacy in IV/V Men
(mortality day 91, FDA analysis)

- Study 32 (N=1,015)
- Men n = 337
- IV/V n = 34
- TIR : 0/15 (0%)
- PBO: 9/19 (47%)
- nominal p = 0.0026
- adjusted p = 0.0624

- Study 29 (N=897)
- Men n = 282
- IV/V n = 32
- TIR : 2/20 (10%)
- PBO: 4/12 (33%)
- nominal p = 0.0758
- adjusted p = 0.6064

Study 32 - Mortality in Men, by Neurograde

Group	PBO	6 mg/kg/d	nominal p value
Men, Day 76			
Low Neurograde (I/II/III)	11/60 (18%)	2/82 (2.4%)	0.002
High Neurograde (IV/V)	9/19 (47.4%)	0/15 (0%)	0.002

Efficacy in IV/V Women
(mortality day 91, FDA analysis)

- Study 65 (N=817)
- IV/V n=235
- TIR : 37/116 (32%)
- PBO: 44/119 (37%)
- nominal p = 0.413

- Study 63 (N=823)
- IV/V n=152
- TIR : 17/69 (25%)
- PBO: 36/83 (43%)
- p = 0.016

Study 63 - Neurograde IV/V

- Baseline imbalances in this subgroup?
- High neurograde subgroup selected while study was ongoing
- Randomization not stratified by low vs. high neurograde
- ~20% of overall study population

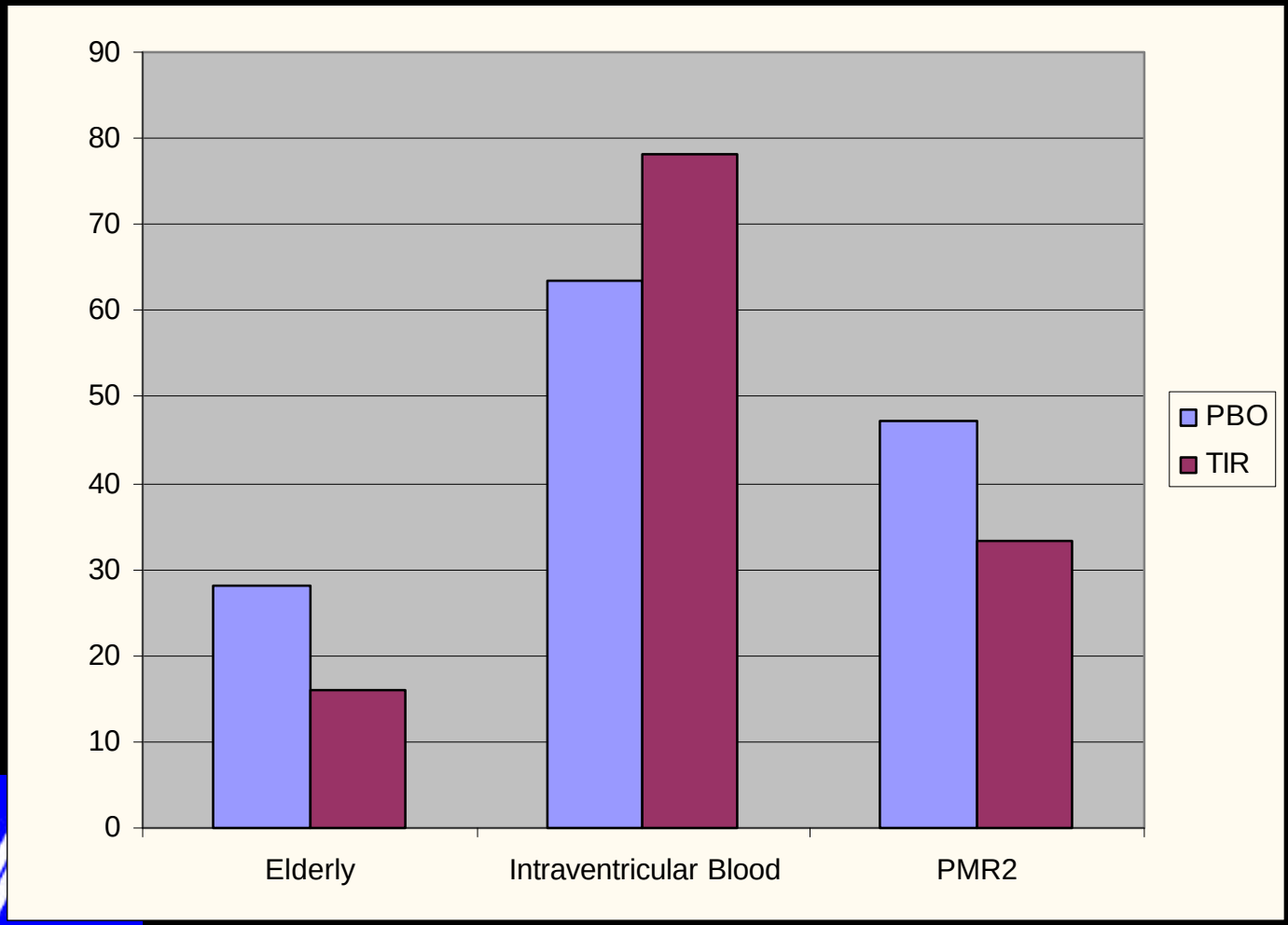
Study 63 - Risk Factors

- Age ≥ 65
- intraventricular blood
- thick SAH clot
- bilateral poor motor response (PMR2)

Study 63 - Risk Factors Present in Placebo Patients (n=413)

Risk Factor	Risk Ratio	p value
Age ≥ 65	1.869	0.0236
Thick SAH clot	1.888	0.0298
IV Blood	1.794	0.0237
PMR2	8.076	0.0001

Study 63 - Distribution of Risk Factors in IV/V Patients

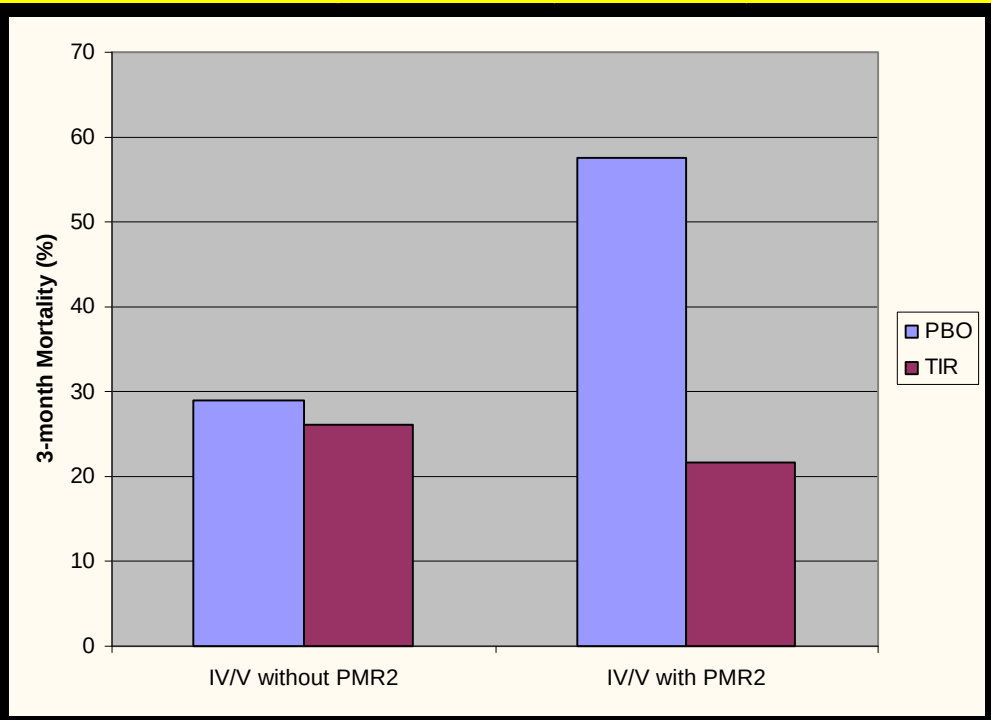


Study 63 - Subgroup Analysis of High Neurograde Patients

Population	Death (%)		Nominal p value[#]
	PBO	TIR	
IV/V without PMR2	13/45 (28.9)	12/46 (26.1)	0.8261
IV/V with PMR2*	23/40 (57.5)	5/23 (21.7)	0.0237

[#] log-rank test

* stratified by presence of intraventricular blood and thick SAH clot



Mortality in High Neurograde

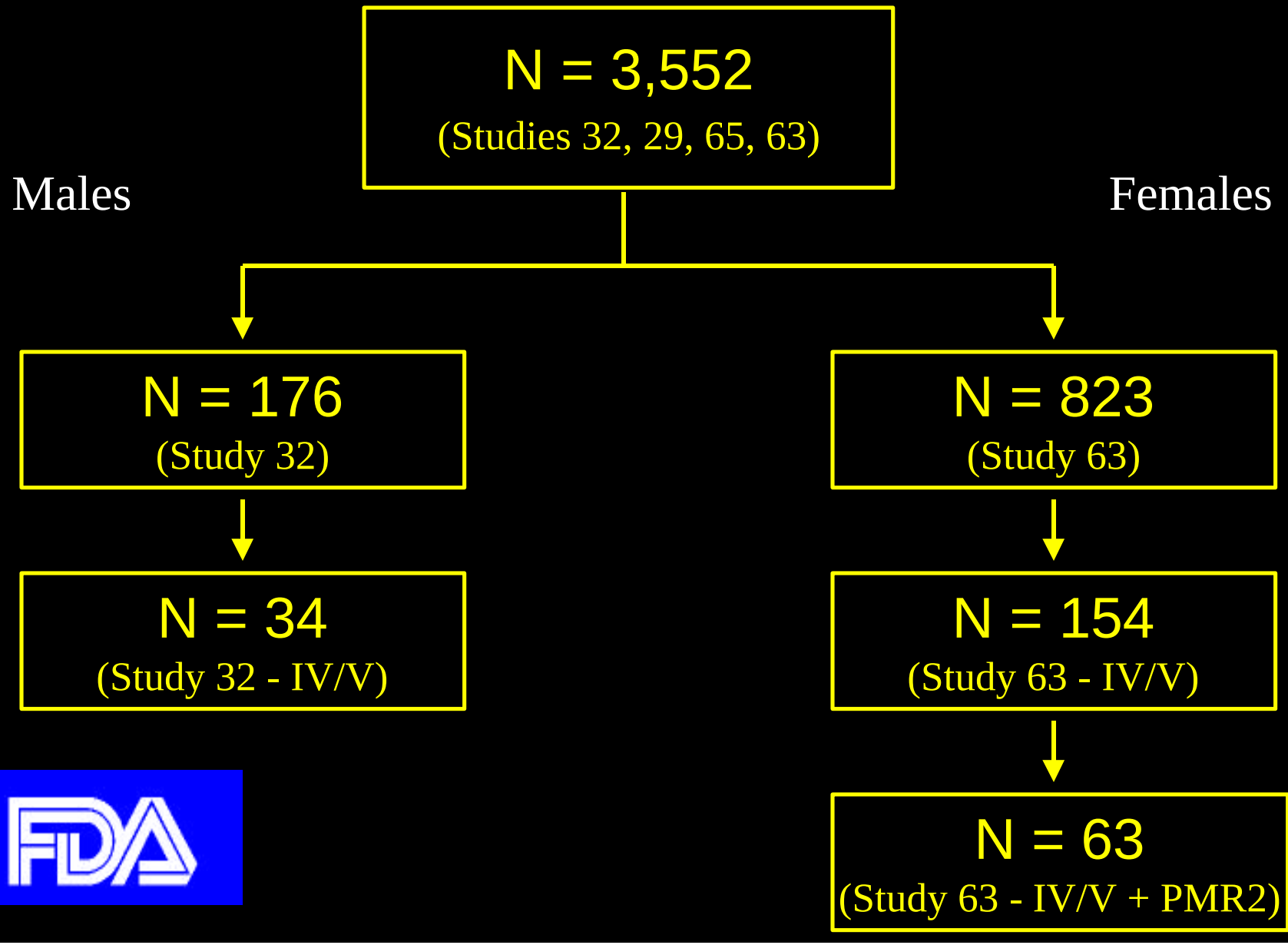
Study	Gender	Analysis	N (IV/V)	PBO (%)	TIR (%)	p value	adjusted p value
32 N=1015	Men	Retro-spective	34	9/19 (47.4)	0/15 (0.0)	0.0026	0.0624[a]
29 N=897	Men	Retro-spective	32	4/12 (33.3)	2/20 (10.0)	0.0758	0.6064[b]
65 N=817	Women	Retro-spective	235	44/119 (37.0)	37/116 (31.9)	0.413	
63 N=823	Women	Pro-spective	152	36/83 (43.4)	17/69 (24.6)	0.016	

(a) adjusted for 3 doses, 2 endpoints (mortality, vasospasm), 2 genders, 2 neurograde subgroups

(b) adjusted for 2 doses, 2 genders, 2 neurograde subgroups

dose in men was 6 mg/kg/d and in women 15 mg/kg/d

Source of Evidence

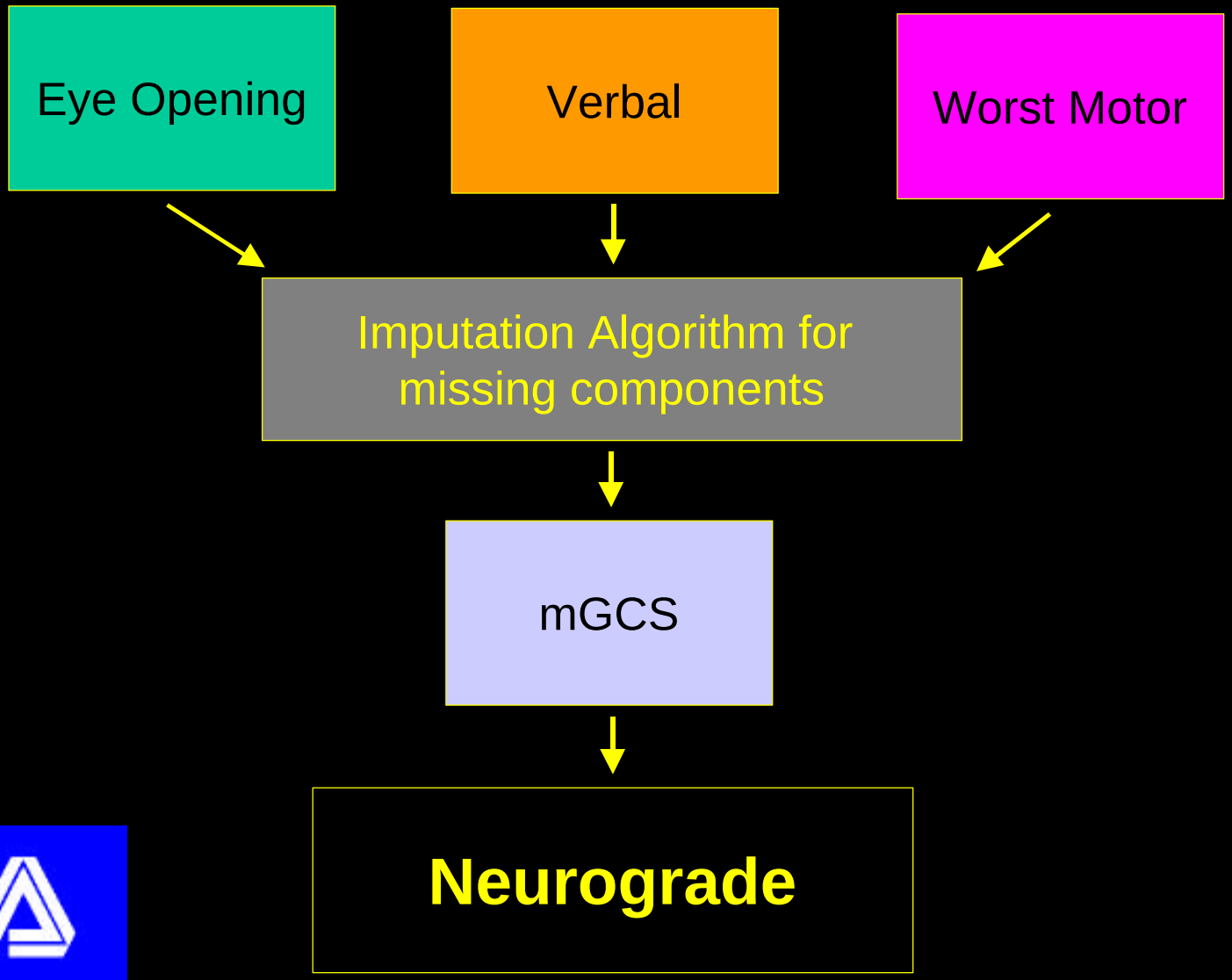


2. The Target Population

- Question: Who should receive the drug?

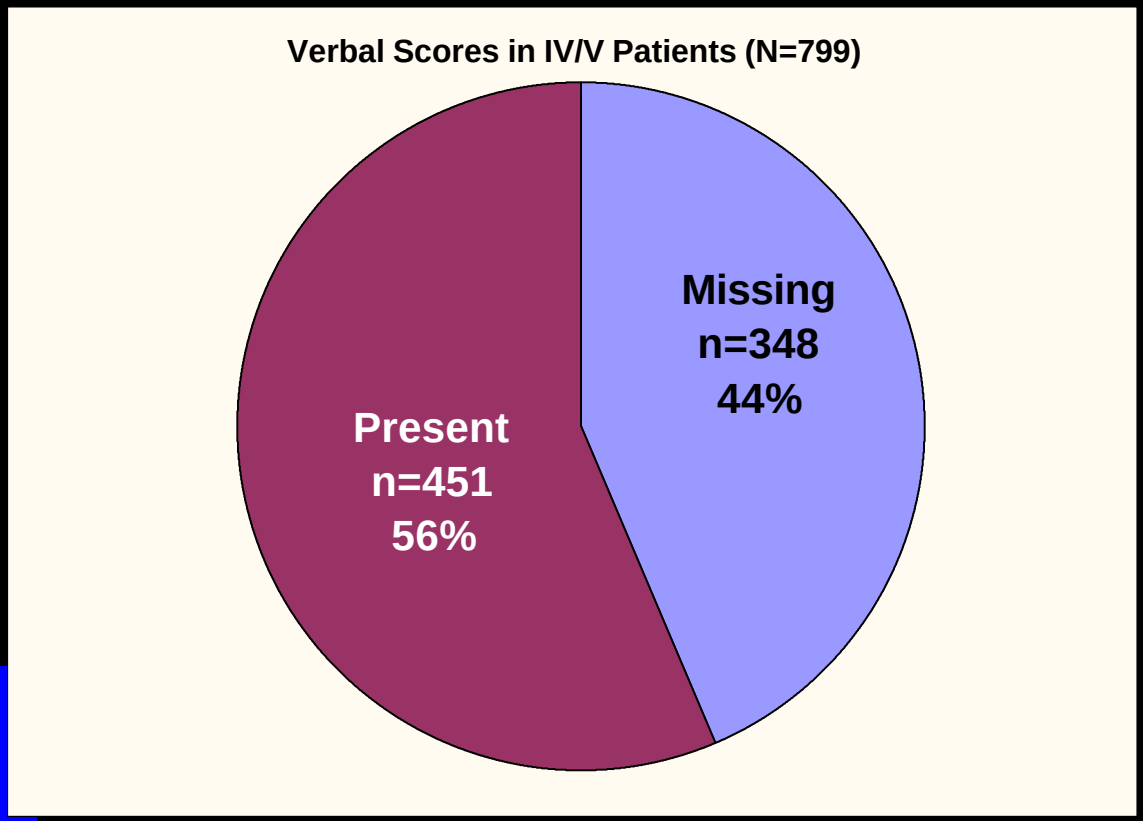
- Answer: Neurogrades IV/V

Neurograde


Eye Opening
Verbal
Worst Motor
Imputation Algorithm for missing components
mGCS
Neurograde

Missing Verbal Scores

- All neurogrades: 13% missing verbal scores
- IV/V patients: 44% missing verbal scores (348/799)



Neurograde Scale

- Not best scale for seriously ill
- almost half in IV/V had missing verbal scores
- Hunt & Hess + Neurograde

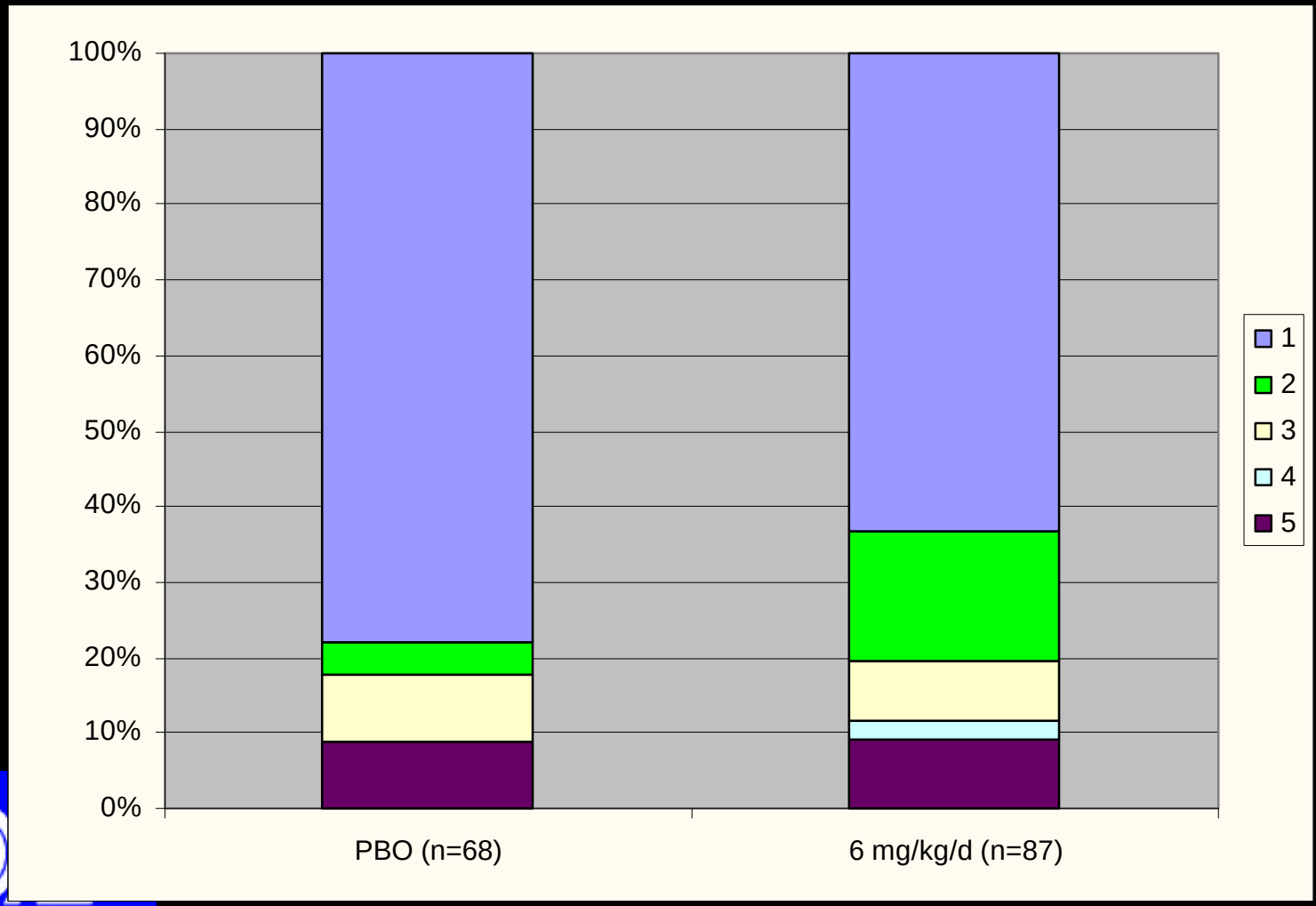
3. Tirilazad in Low Neurograde

- Study 63 - 3-month GOS

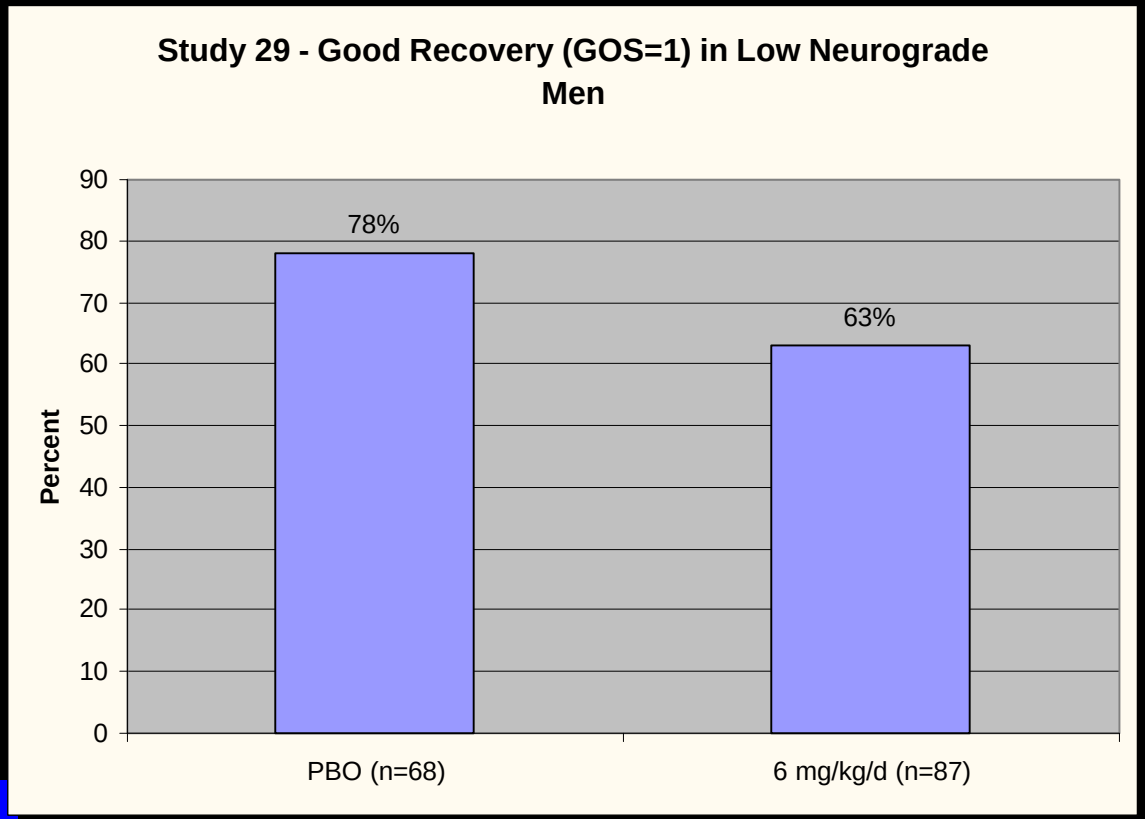
GOS Level	Odds Ratio*	95% CI	p-value
Neurograde I-III – Treatment Comparison Unadjusted			
Composite	1.35	0.98-1.84	0.064
Good Recovery	1.32	0.95-1.82	0.095
Favorable Outcome	1.52	1.03-2.24	0.037
Vegetative Death	1.29	0.78-2.15	0.324

* odds ratio < 1 favors drug

Study 29 - Distribution of GOS in Low Neurograde Men



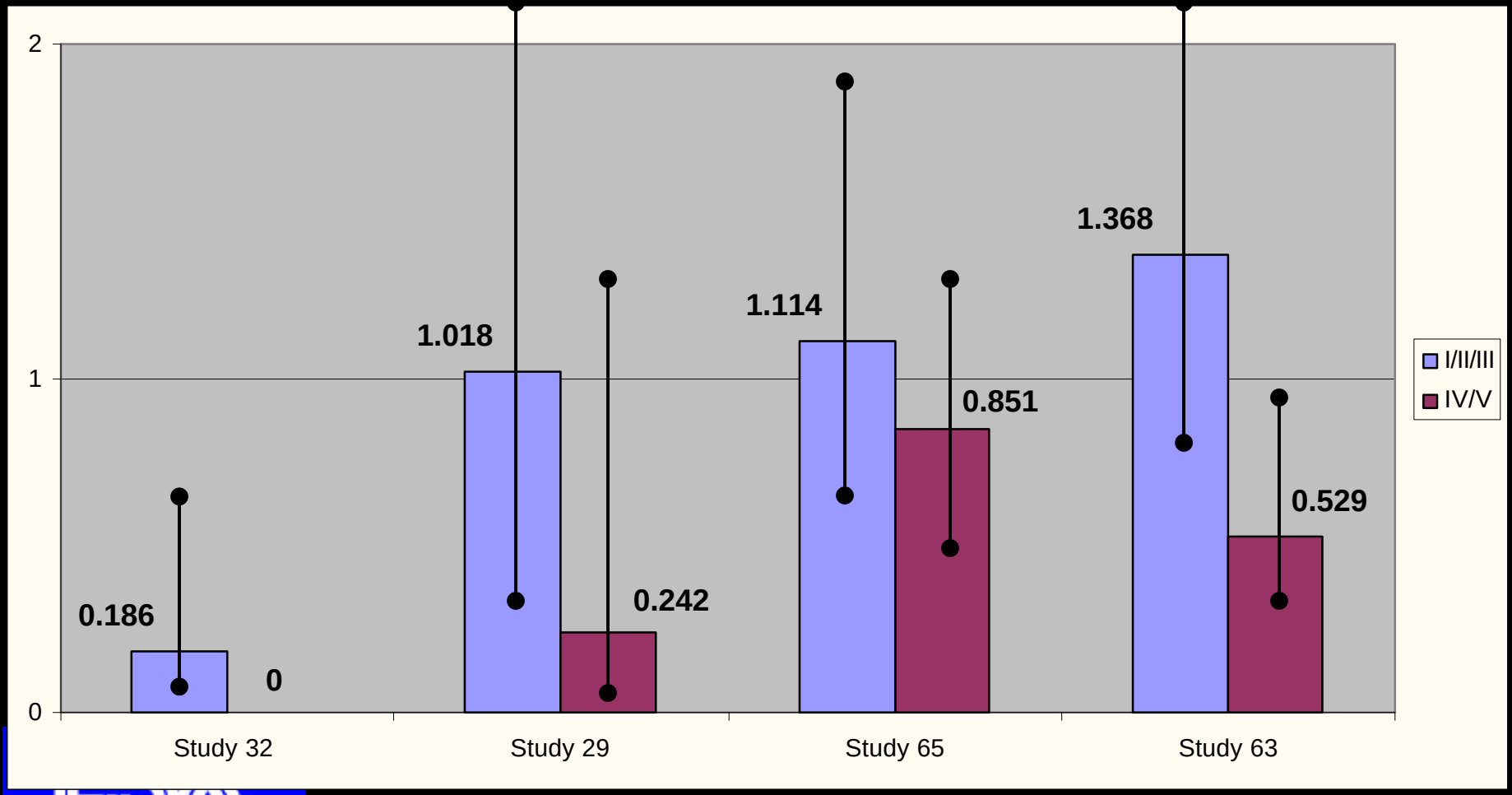
Study 29 - Good Recovery in Low Neurograde Men



nominal p=0.05 (chi-square)

Relative Risk - Mortality

Low vs. High neurogrades



TIR	2/85	0/15	8/88	2/20	33/286	37/118	35/341	17/69
PBO	11/61	9/19	6/68	4/12	20/288	44/125	25/328	36/85

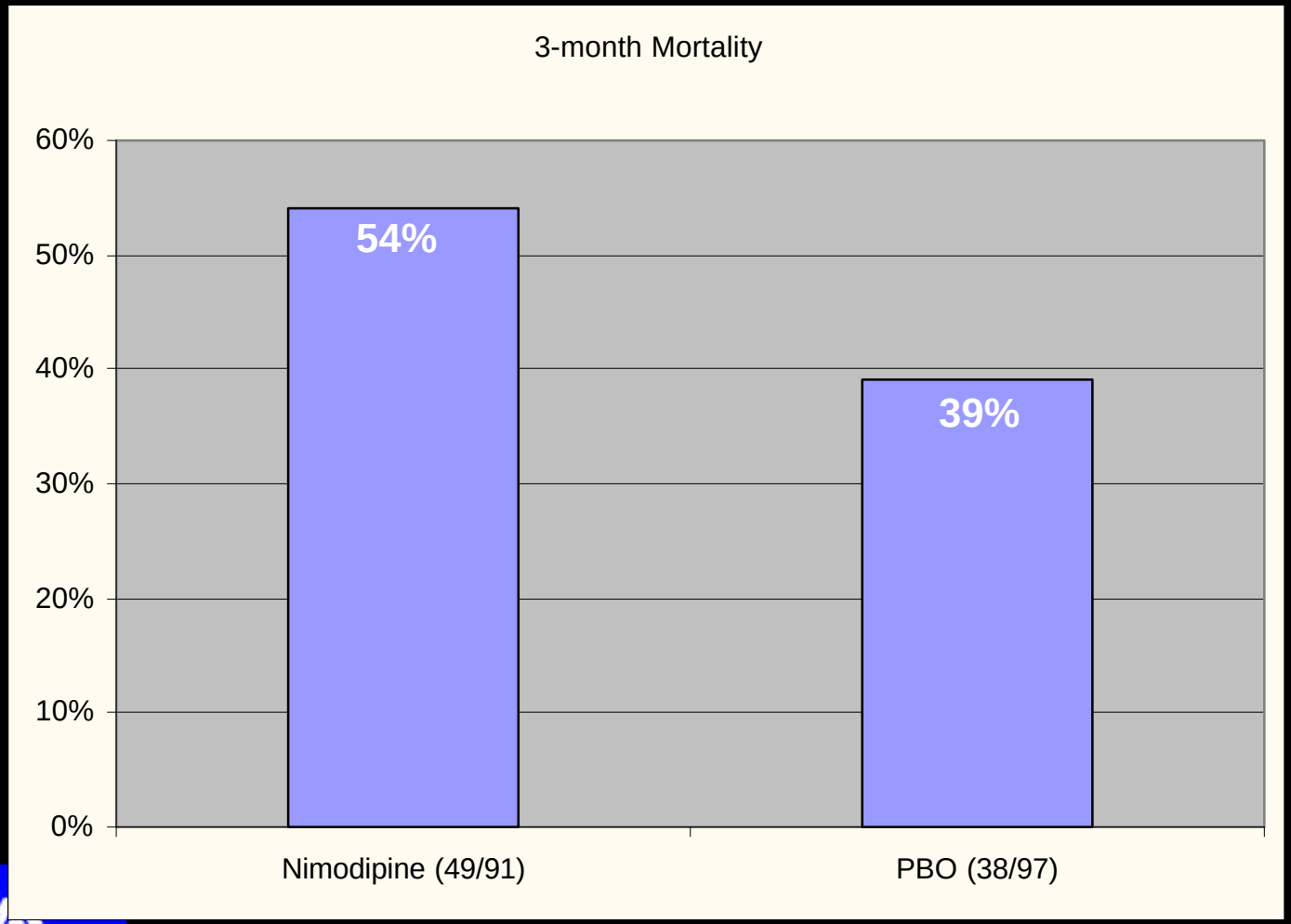
4. Nimodipine

- All patients received nimodipine
- Approved for H&H I-III only
- Negative effect on mortality in IV/V?
- Petruk, *et al*, "Nimodipine Treatment in Poor Grade Aneurysm Patients," J Neurosurg, 1988;22:484-491 (also described in nimodipine product labeling)

Petruk, et al.

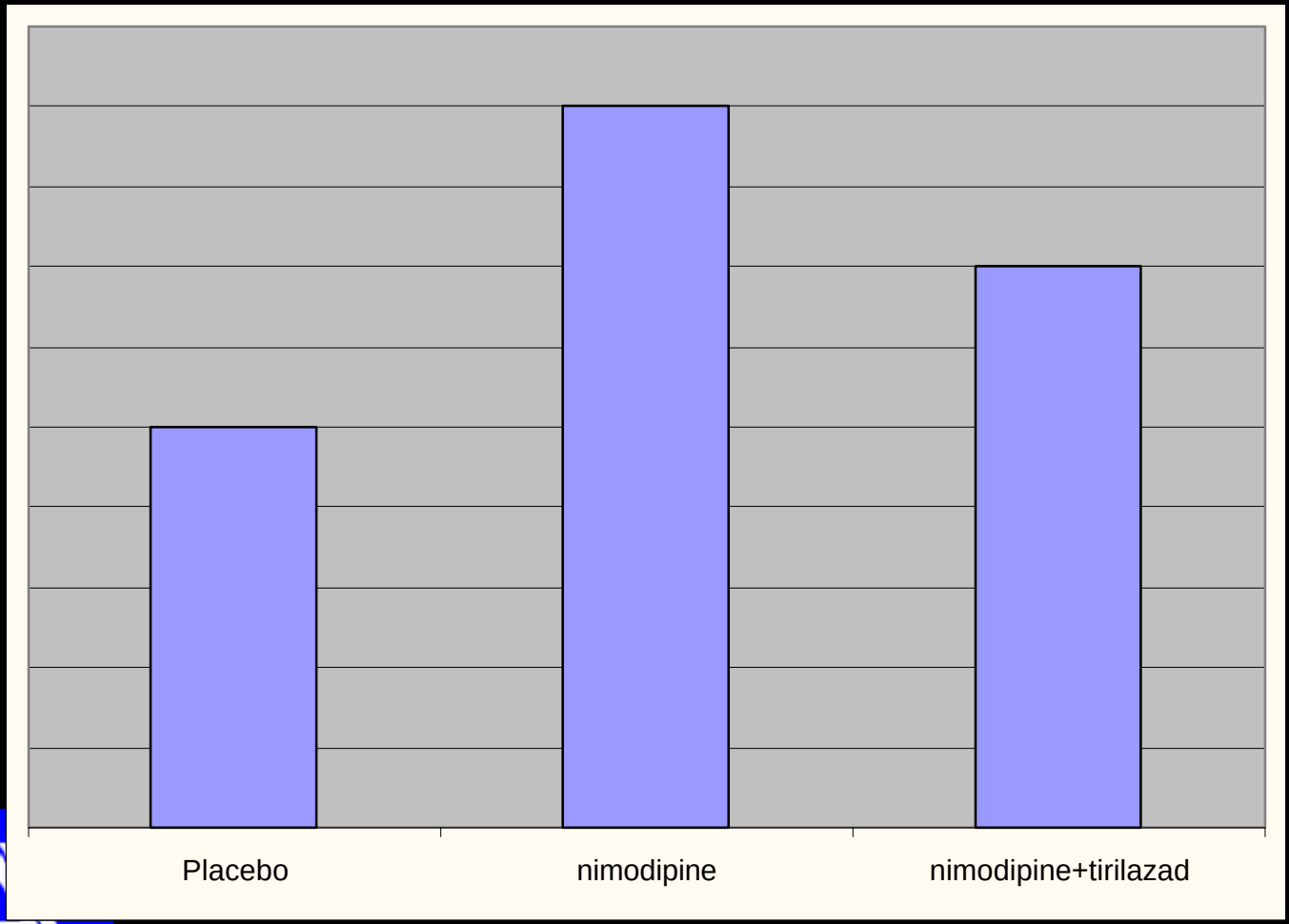
- Randomized, double-blind, placebo-controlled, multicenter
- Hunt & Hess III-V
- N=188
- 90 mg q 4 hrs (21 days)
- 3-month GOS
- mortality

Petruk, et al, (cont'd)



nominal p=0.044 (chi square)

Nimodipine Effect ???



Summary

1. Is there substantial evidence of efficacy?
2. Can clinicians identify the target population easily and accurately?
3. Is there a risk to low neurograde patients?
4. What is the effect of concomitant nimodipine in high neurograde patients?