Peripheral & Central Nervous System Drugs Advisory Committee

April 29, 1999

FREEDOX®
(tirilazad mesylate)
Pharmacia & Upjohn

FREEDOX®
[Pharmacia and Upjohn: NDA 20-399]

• Introduction - SAH Development Program - Past and Present Issues	Mark Corrigan, M.D. VP, Global Clinical Research Pharmacia & Upjohn
• Risk Benefit Assessment: SAH - Response to Specific FDA Comments	Lawrence F. Marshall, M.D. Professor & Chief Division of Neurological Surgery University of California San Diego California, USA
• Response to Questions	Mark Corrigan, M.D. VP, Global Clinical Research Pharmacia & Upjohn

Indication

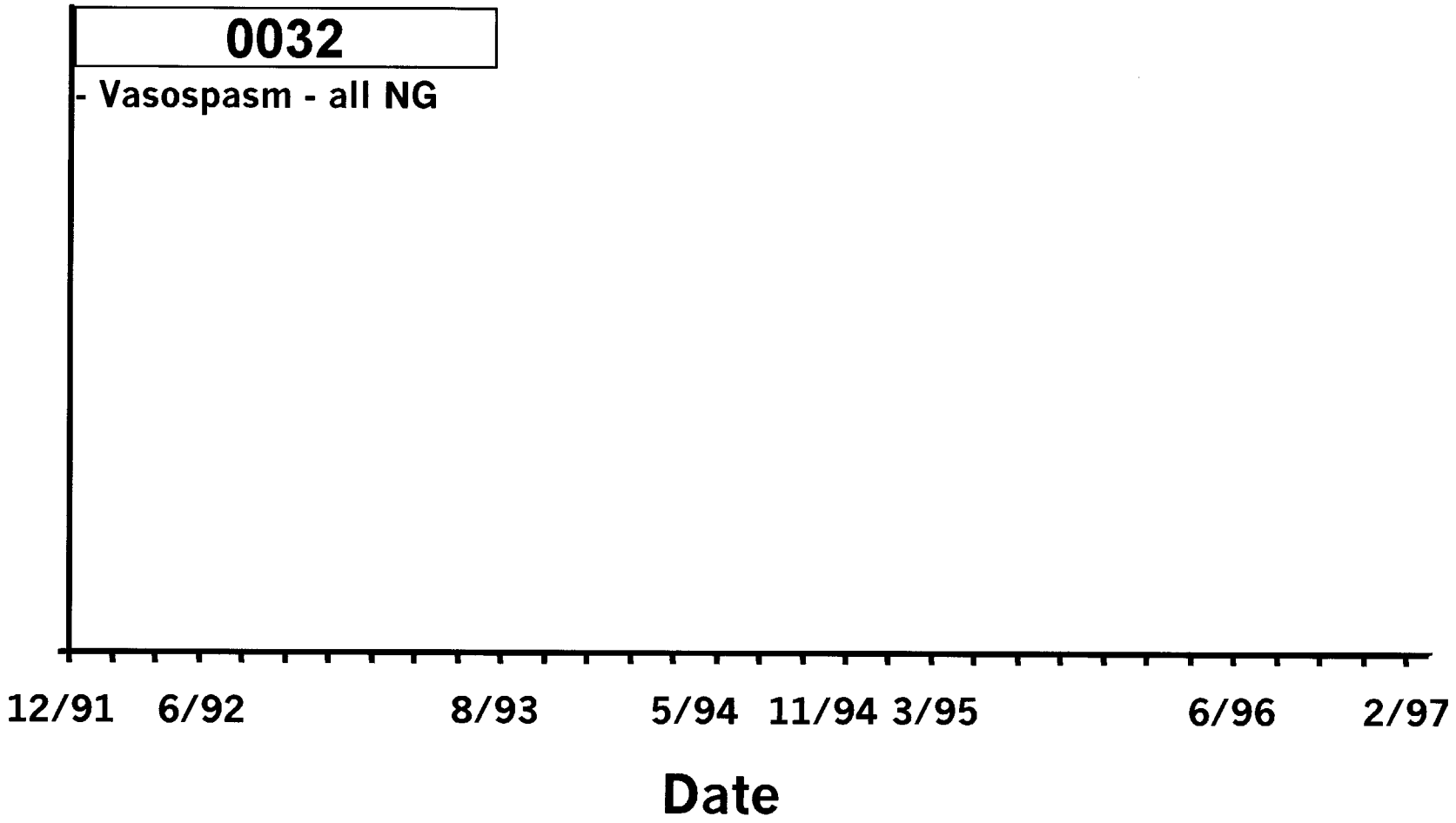
- Tirilazad mesylate (TIR) is indicated for the treatment of aneurysmal subarachnoid hemorrhage (SAH) to improve survival and functional outcome in patients with poor neurological function following the initial hemorrhage
- Begin treatment within 48 hours of initial hemorrhage, preferably prior to surgery

Scope of TIR Clinical Program

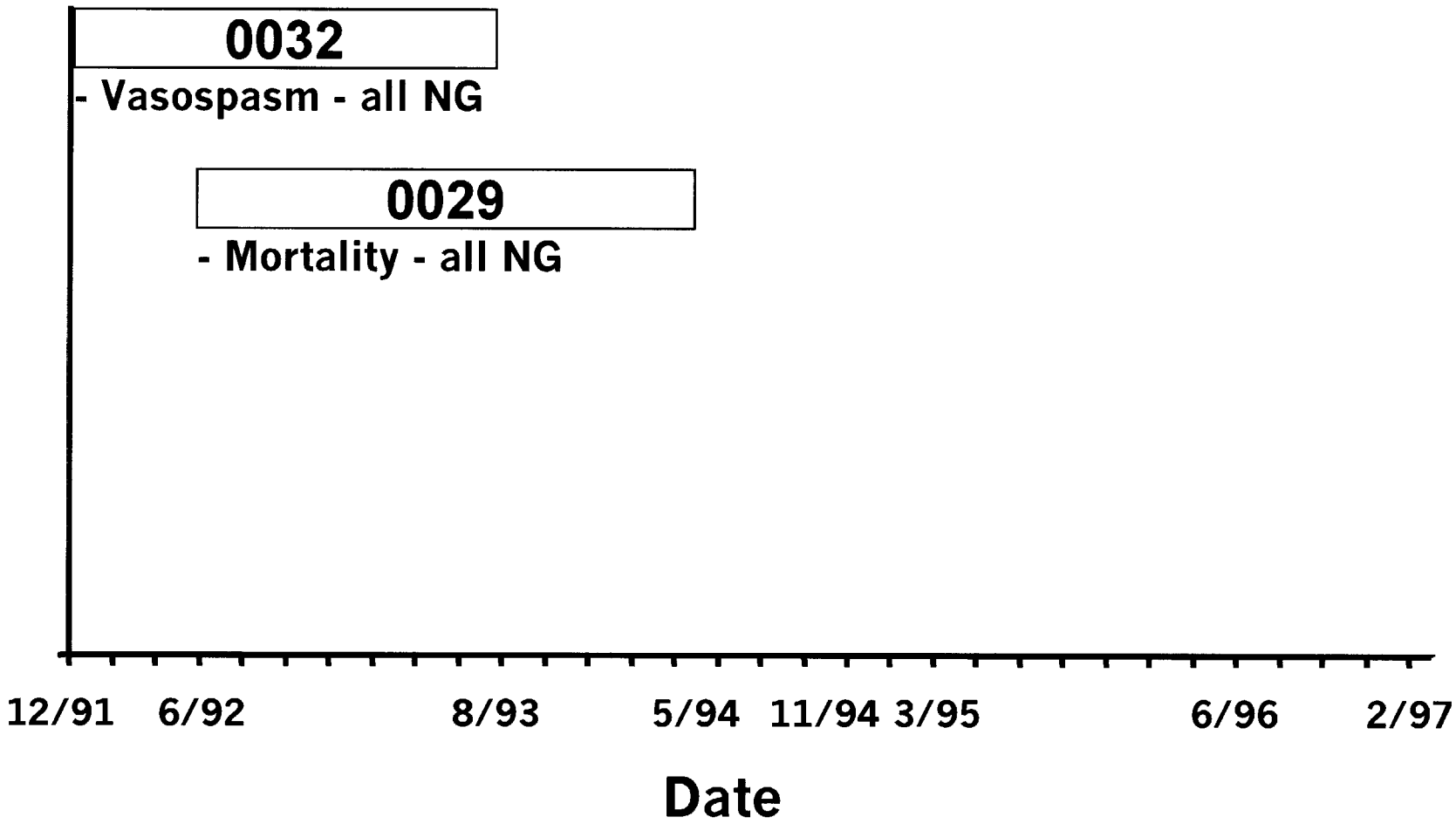
Study Phase	No. of Studies	Patients Dosed VEH	TIR	Total
I	28	101	572	673
II/III Vehicle- and Nimodipine-Controlled SAH	7	1448	2371	3819
II/III Vehicle-Controlled SAH	1	77	153	230
II/III Uncontrolled SAH	3	NA	591	591
II/III Controlled Head Injury	5	1205	1283	2488
II/III Uncontrolled Head Injury	2	NA	20	20
II/III Stroke	6	817	893	1710
II/III Contrast Nephropathy	1	38	37	75
Spinal Cord Injury†	2	NA	181	181
Overall Total	55	3686	6101	9787

† Methylprednisolone sodium succinate control for protocol 0028

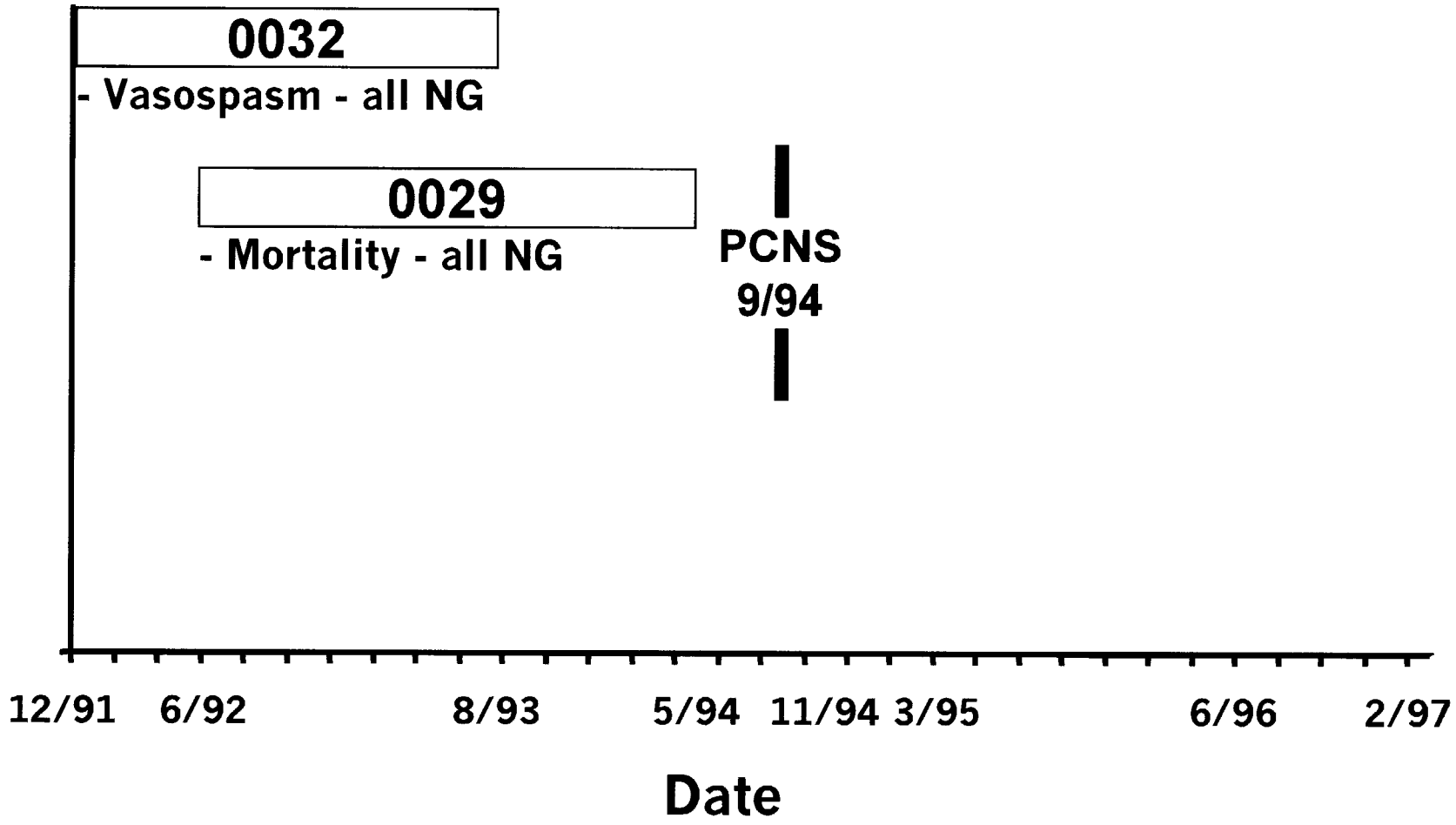
SAH Development Timeline



SAH Development Timeline



SAH Development Timeline



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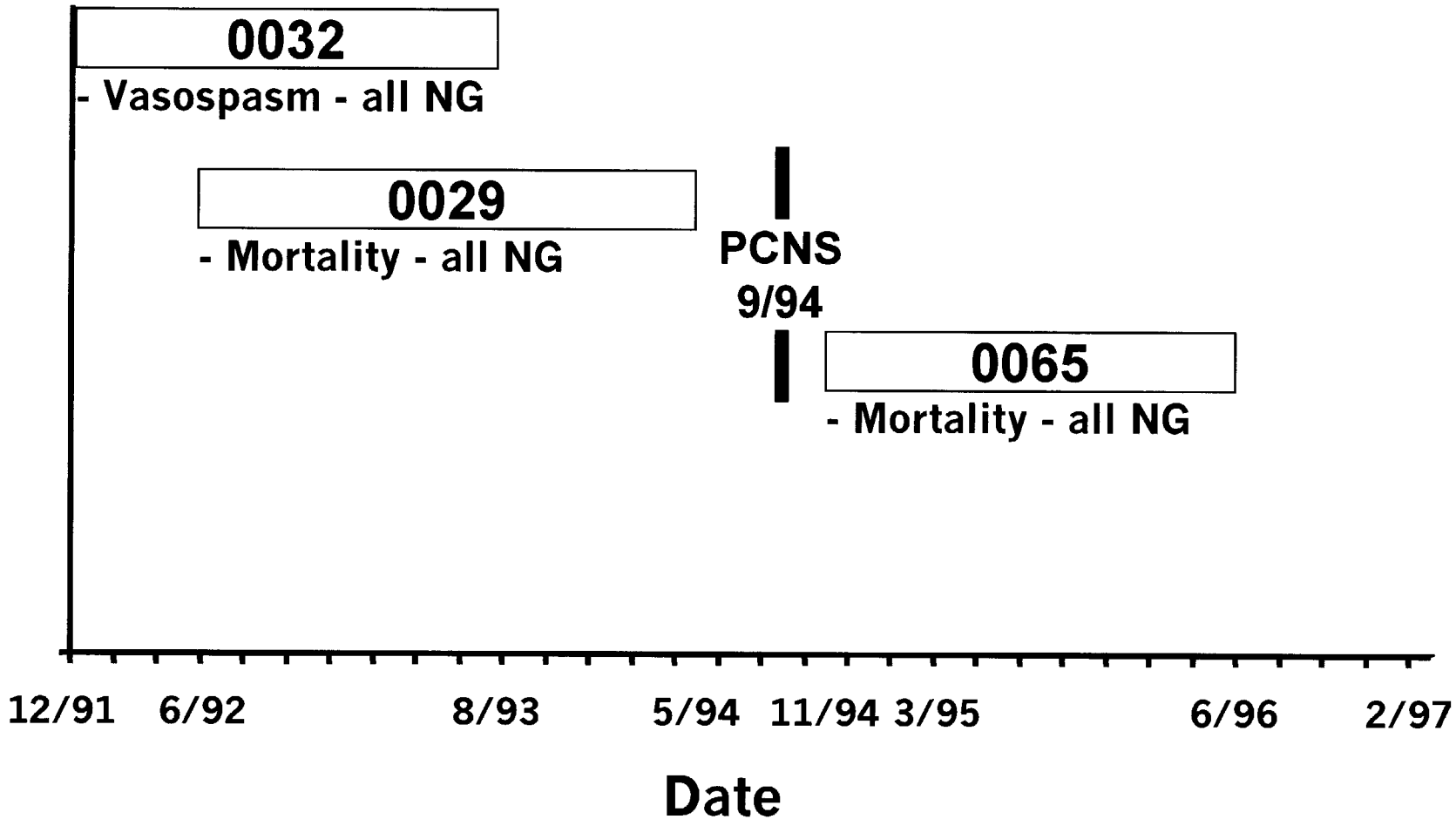

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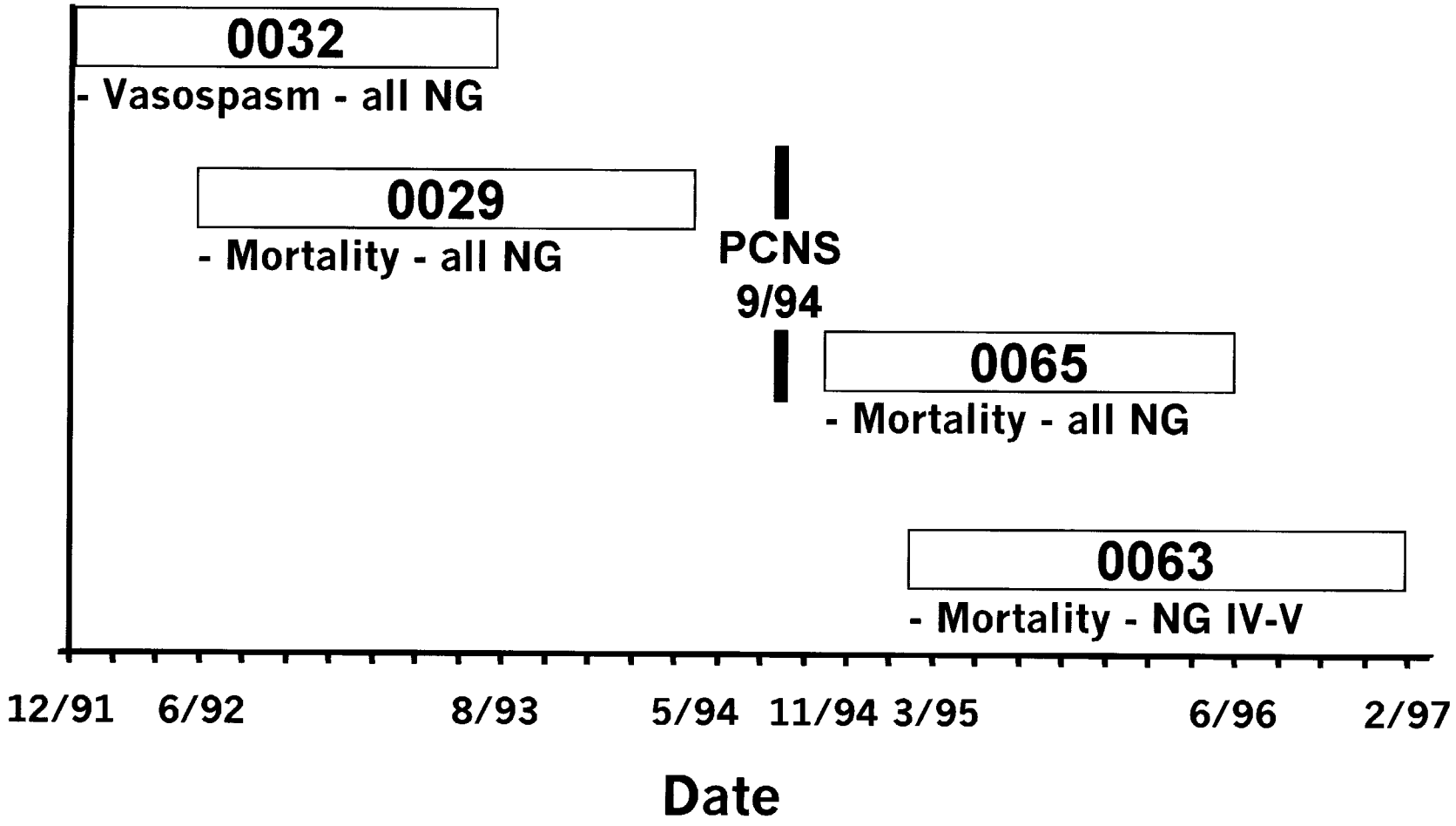
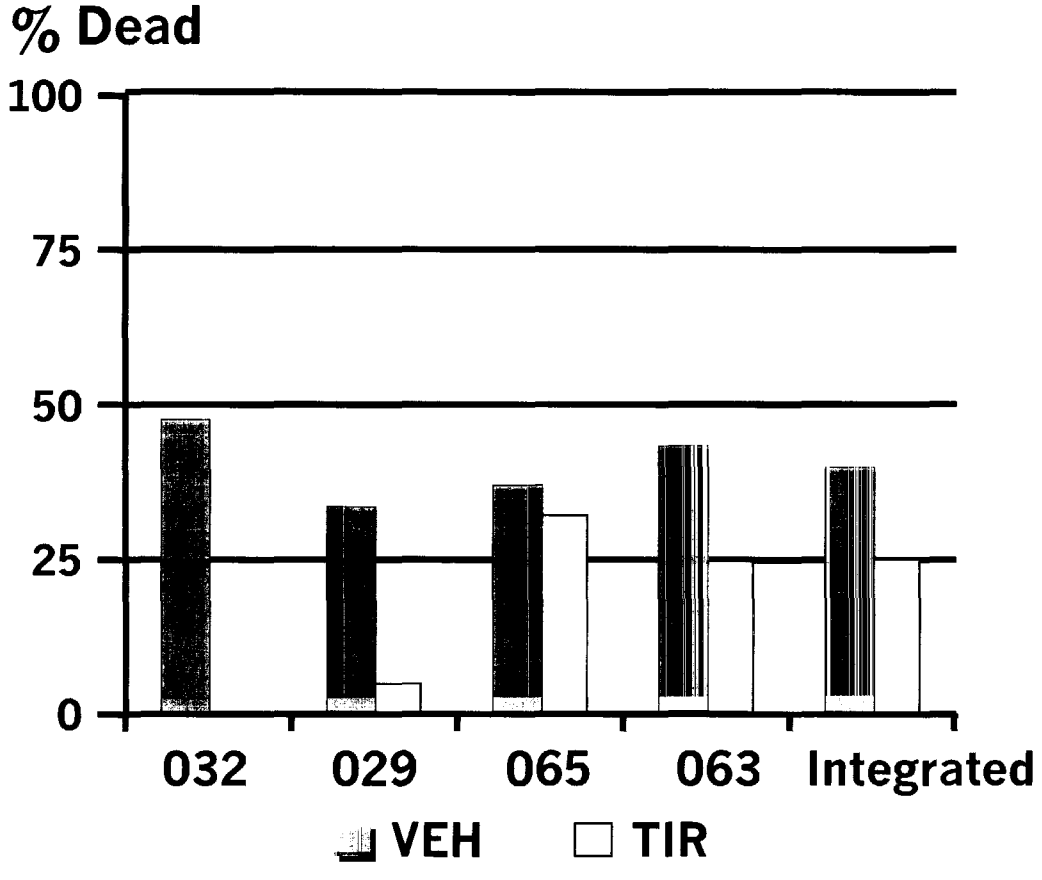


Body of Evidence
3-Month Mortality NG IV-V



TIR 6 Males (0032, 0029), TIR 15 Females (0065, 0063)

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FDA Evaluation
Key Issues

- Justification for integrated analyses
- Efficacy
- Identification of target population
- Complementary increased risk in NG I-III
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3-Month Mortality
NG IV-V

	No. Reporting		% Dead		
Protocol	VEH	TIR†	VEH	TIR	p-Value
0032	19	15	47	0	0.002‡
0029	12	20	33	5	0.033‡
0065	119	116	37	32	0.413
0063	83	69	43	24	0.016

† TIR 6 Males (0032, 0029), TIR 15 Females (0065, 0063)

‡ Critical p-Value <0.05 due to multiple testing

Prespecified Prognostic Factors for SAH Studies

- Level of consciousness (mGCS)
- Presence of intraventricular blood on CT scan
- Time from SAH to admission
- SAH clot thickness
- Site of ruptured aneurysm
- Number of pre-existing medical conditions
- Pretreatment systolic blood pressure
- Age

Admission Angiogram
Ruptured Aneurysm Location - NG IV-V

Protocol	% Posterior†	
	VEH	TIR‡
0032	0	20
0029	0	26
0065	10	20
0063	14	23

† Posterior Cerebral, Vertebral or Basilar

‡ TIR 6 Males (0032, 0029), TIR 15 Females (0065, 0063)

Admission CT Scan
NG IV-V

Protocol	% Intraventricular Hematoma	
	VEH	TIR†
0032	74	73
0029	83	90
0065	54	63
0063	64	78

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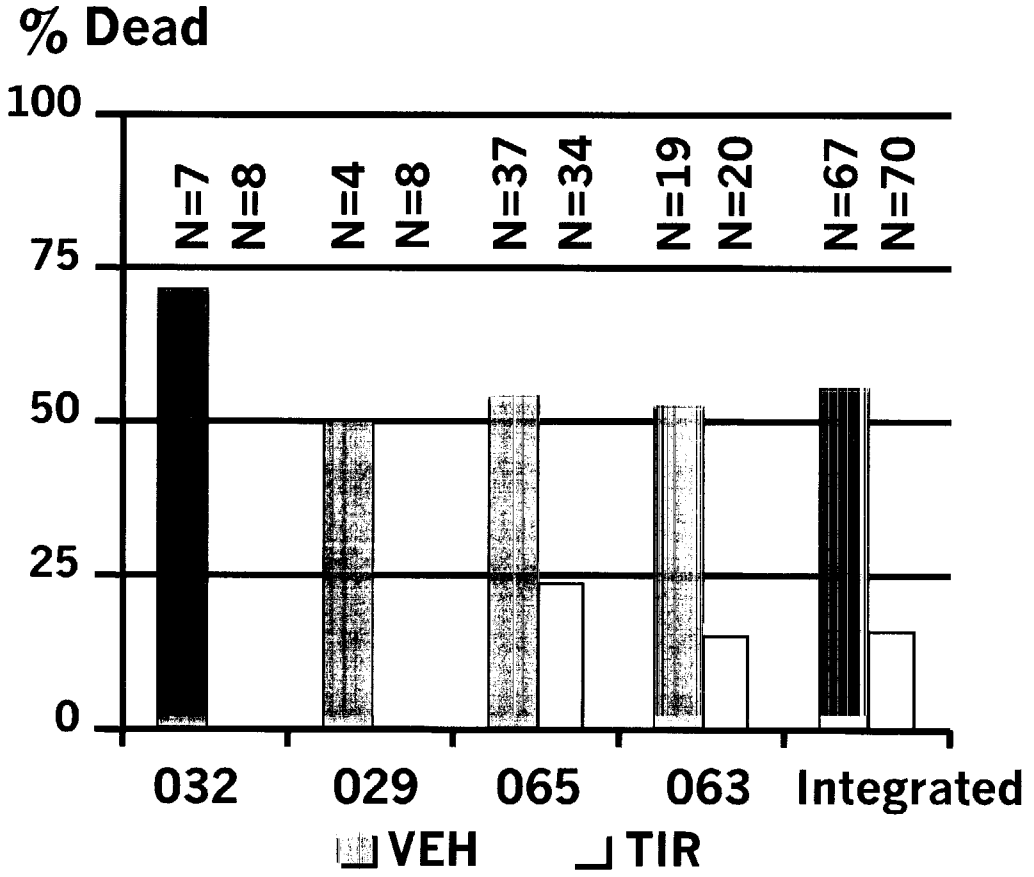
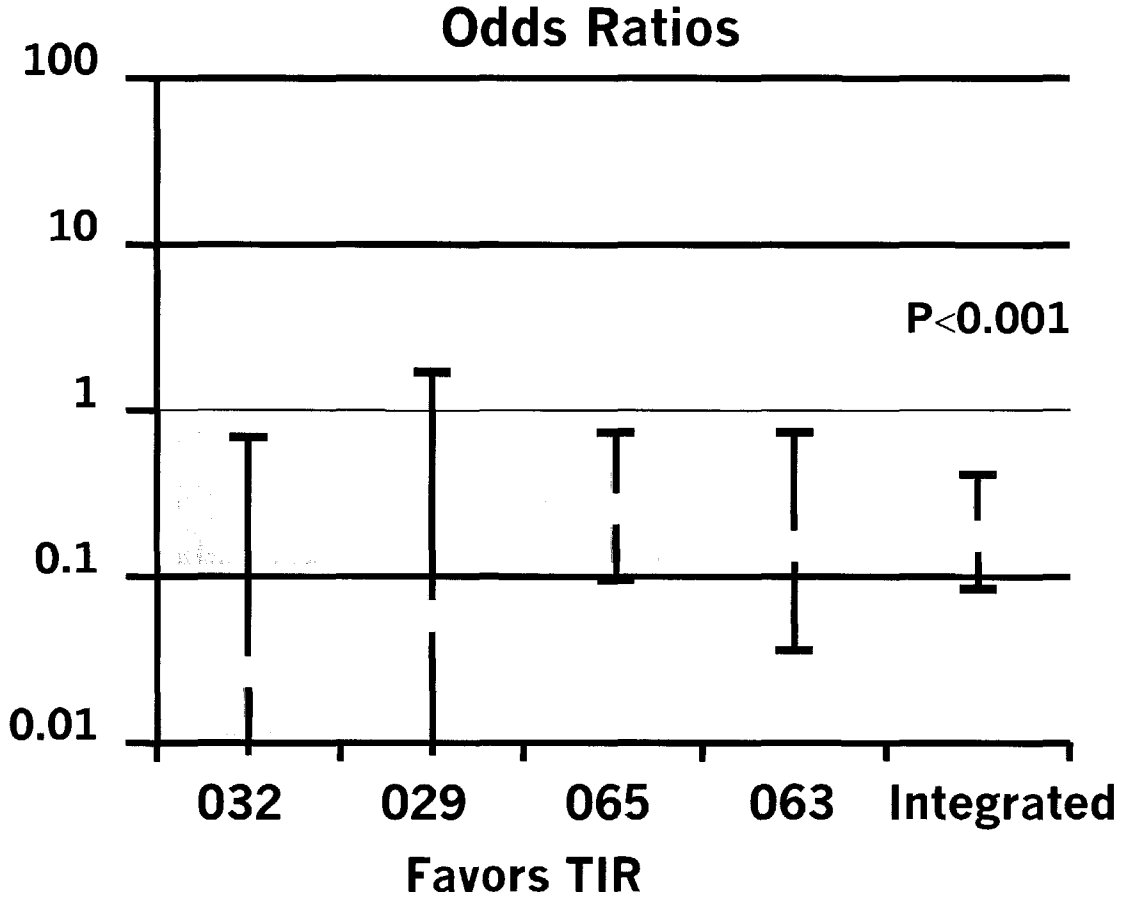
3-Month Mortality
NG IV-V Dosed Within 24 Hours



* Mechanism

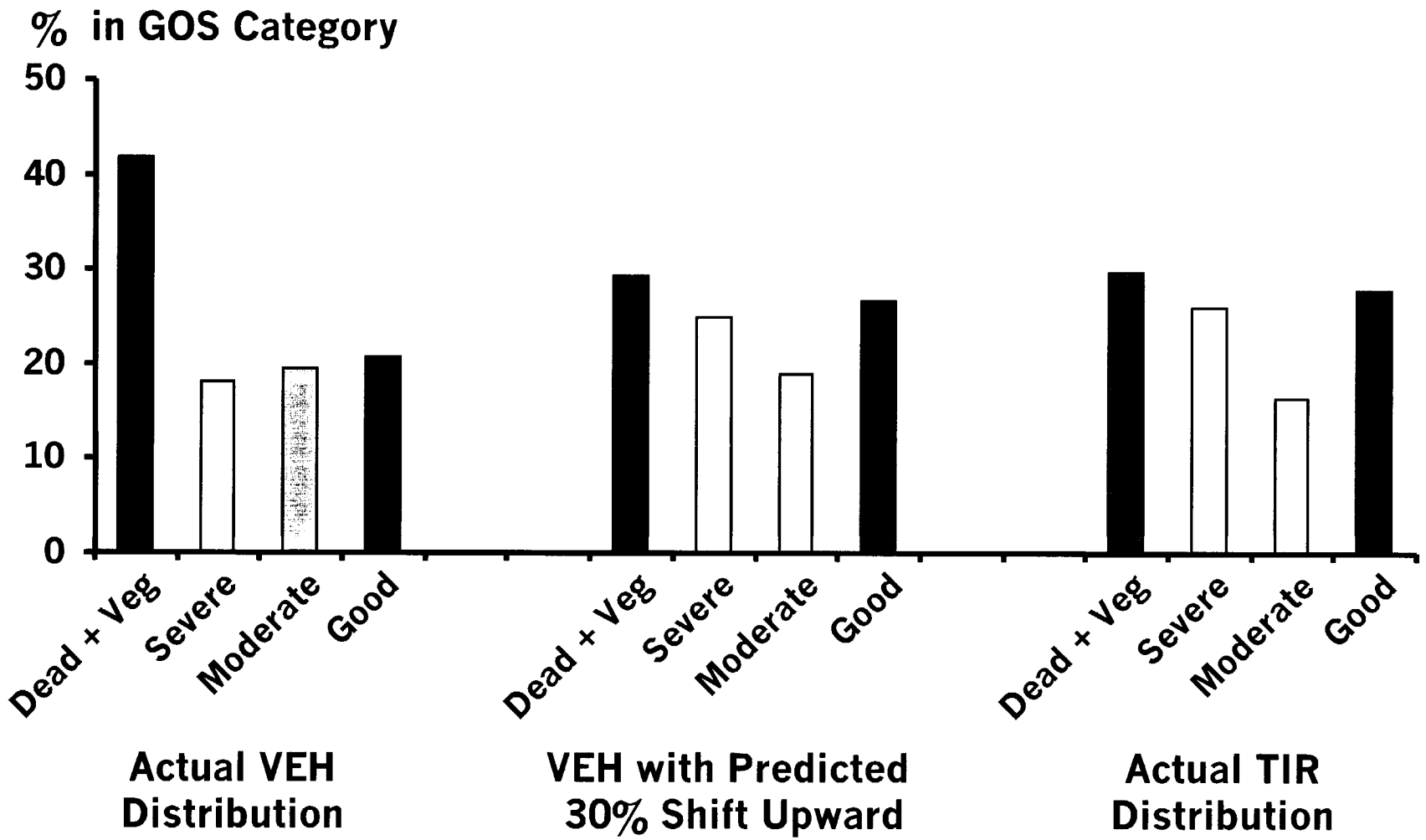
TIR 6 Males (0032, 0029), TIR 15 Females (0065, 0063)

3-Month Mortality
NG IV-V Dosed Within 24 Hours



TIR 6 Males (0032, 0029), TIR 15 Females (0065, 0063)

3-Month GOS - Shift Model
NG IV-V



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3-Month Mortality
NG IV-V: Best Motor Score ≤5

Protocol	% of Total N
0032	97.1
0029	87.5
0065	93.6
0063	89.5
Integrated	92.1

3-Month Mortality
All NG: Best Motor Score $\leq$ 4

	N		% Dead	
Protocol	VEH	TIR	VEH	TIR
0032	15	14	53.3	0.00
0029	7	9	28.6	11.1
0065	91	79	39.6	38.0
0063	56	46	51.8	26.1
Combined	270	148	44.4	29.0

Effect of Classification Scheme on Mortality (IV-V)

Method	OR	p-Value
mGCS	0.56	0.001
WFNS	0.67	0.02
GCS Best Motor Score	0.48	0.001

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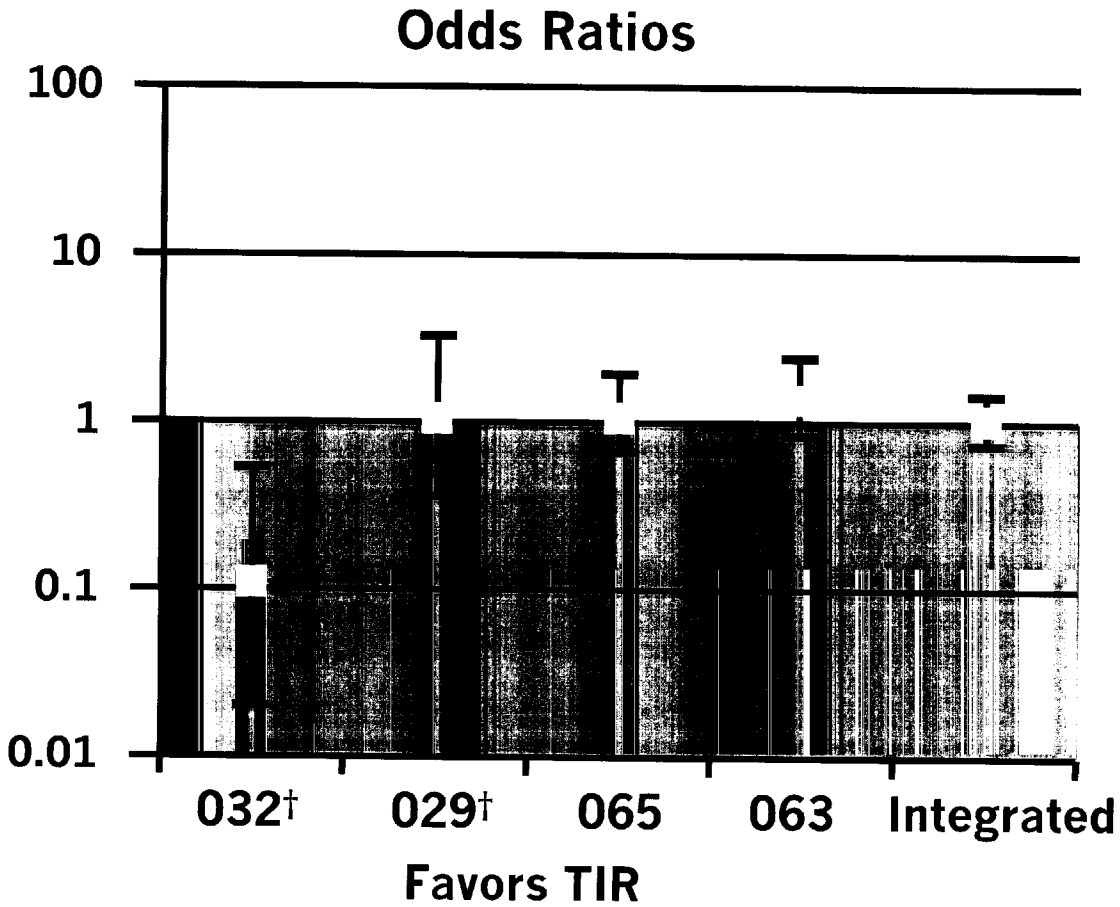
3-Month Mortality
NG I-III 0065 & 0063

Protocol	No. Patients VEH	No. Patients TIR	% Dead VEH	% Dead TIR	p-Value
0065	275	273	10.9	12.1	NS
0063	321	334	7.8	10.5	NS
Combined	596	607	9.2	11.2	NS

Mortality
NG I-III



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3-Month Mortality
All NG: Best Motor Score = 6

	N		% Dead	
Protocol	VEH	TIR	VEH	TIR
0032	57	80	17.5	2.5
0029	65	86	7.7	8.6
0065	253	265	11.5	10.6
0063	311	313	8.7	9.6
Combined	686	744	10.4	9.0

3-Month Mortality
All NG: Best Motor Score = 5 or 6

	N		% Dead	
Protocol	VEH	TIR	VEH	TIR
0032	64	83	18.8	2.4
0029	72	96	11.1	8.3
0065	303	310	12.5	12.9
0063	348	357	9.2	11.2
Combined	787	846	11.4	10.6

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Use of Nimodipine

- In SAH patients (Hunt and Hess I-III); improves neurological outcome and reduces the incidence and severity of ischemic deficits
- Often not used in Hunt & Hess I
- Standard of care worldwide in Hunt & Hess IV-V

FDA Evaluation
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Stroke Studies
Protocols 0088 & 0081

- Double blind, vehicle controlled, randomized (1:1)
- Stratified by gender
- Dosing - 300 mg within 4 hr. (0088) or 6 hr. (0081) followed by:
  - men 10 mg/kg per day
  - women 12 mg/kg per day
- Primary endpoint
  - 3 month expanded Barthel Index
  - Secondary endpoints GOS, UNSS/NIH-SS, safety
- Data Safety Monitoring Board (DSMB)

Stroke Studies
Program Overview

- 0088 Early termination by interim analysis
  - Futility analysis
  - Impression of higher mortality at 10 days in TIR group
  - Not evident on final analysis
- 0081
  - Impression of lower mortality at 10 days in TIR group
- Program discontinued

Mortality
Dosed Patients 0088 & 0081

Study Period	VEH		TIR	
	n (N)	%	n (N)	%
Day 10	18 (235)	8	26 (233)	11
3 Months	47 (235)	20	45 (233)	19

3-Month Causes of Death Dosed Patients

	081		088		Combined	
	VEH	TIR	VEH	TIR	VEH	TIR
	N=62	N=57	N=173	N=176	N=235	N=233
Direct Effect Adm Infarc	7	5	7	8	14	13
Extension of Adm Infarc	3		1	5	4	5
Hemorrhagic Conversion	2		1	5	3	5
Increased ICP				1		1
Intraparenchymal Hemor		1				1
Medical Complications	7	5	17	13	24	18
New Stroke	1				1	
Presumed Cardiac Arrest				1		1
Surgical Complications			1		1	
Unknown		1				1
Total	20	12	27	33	47	45

Head Injury
Pivotal Studies

	Number of Patients		
Protocol	VEH	TIR	Total
0017	559	570	1129
0036	558	562	1120

Head Injury
DSMB Recommendations

- Higher mortality detected in TIR group (study 0017). Discontinuation advised (>95% enrolled)
- Equally large study (0036) showed no difference in mortality or adverse events

Head Injury
0017 Severe Stratum: Baseline Imbalances

Prespecified Prognostic Covariates	%		p-Value
	VEH	TIR	
Pupil reactivity (both non-reactive)	22	29	0.037
Presence of SAH (yes)	42	47	0.138
Pretreatment hypotension (yes/suspected)	21	26	0.133

- intracranial mass lesions

Head Injury
0017 Severe Stratum: Pupil Response

Variable at baseline	VEH N=402 n	VEH N=402 %	TIR N=404 n	TIR N=404 %	p-Value
Both pupils non-reactive	90	22	117	29	0.037
One pupil non-reactive	53	13	62	15	
Both pupils reactive	259	65	225	56	

SAH Program
Methodology to Detect Increased Risk

- Mortality
- Discontinuation
- Frequency of adverse events
- Serious adverse events

Selected Adverse Events Leading to Discontinuation

	VEH		TIR 6		TIR 15	
Patients Dosed	1445		644		815	
Patients Discontinued	90		67		36	
Medically Equivalent Term	n	%	n	%	n	%
Cerebral Vasospasm	--	--	--	--	--	--
Cerebral Infarction	--	--	--	--	2	0.20
Brain Edema	4	0.30	4	0.60	3	0.36
Intracranial Hypertension	1	0.06	--	--	4	0.40
Hydrocephalus	--	-	--	--	--	--
Pneumonia	--	--	--	--	--	--
Lung Edema	2	0.10	1	0.20	4	0.40

Selected 14-Day Adverse Events with Frequencies ≥10%

Medically Equivalent Term	% VEH (N=1445)	TIR 6 (N=644)	TIR 15 (N=815)
Cerebral Vasospasm	31	25	29
Cerebral Infarction	17	16	16
Brain Edema	13	11	15
Intracranial Hypertension	8	9	7
Hydrocephalus	10	10	9
Pneumonia	18	19	15
Lung Edema	10	10	12

14-Day Selected Serious Adverse Events

Medically Equivalent Term	% VEH (N=1445)	TIR 6 (N=644)	TIR 15 (N=815)
Hydrocephalus	1.9	0.8	1.7
Sepsis	1.5	1.9	1.0
Brain edema	3.8	2.2	4.0
Intracranial hemorrhage	2.0	2.5	2.7
Cerebral infarction	7.3	4.8	6.9
Hypertension intracranial	2.2	1.2	2.3
Cerebral vasospasm	8.2	6.2	8.3
Surgical complications neuroworsening	2.8	4.0	3.3
Surgical complications intracranial bleeding	1.6	1.9	0.5
Pneumonia	1.5	1.9	0.9

14-Day Adverse Events by Body Systems (1 of 2)

Body System	% VEH (N=1445)	TIR 6 (N=644)	TIR 15 (N=815)
Nervous	65	73	59
Metabolic & Nutritional	61	57	66
Body General	42	38	47
Hemic & Lymphatic	38	38	46
Respiratory	36	38	40
Cardiovascular	38	34	39
Urogenital	26	21	29

14-Day Adverse Events by Body Systems (2 of 2)

Body System	% VEH (N=1445)	TIR 6 (N=644)	TIR 15 (N=815)
Reaction Unevaluable (Surgical Complications)	18	21	16
Digestive	20	13	31
Infusion Site Disorders	11	15	13
Skin	6	4	14
Special Senses	7	4	10
Endocrine	6	3	5

FREEDOX®
Safety Conclusions

- Serious cardiac and pulmonary adverse events occurred at a rate expected in seriously ill SAH patients
- Good safety profile for CNS events
- No clinically relevant changes in ECGs or in cardiac, liver, or renal laboratory results

FREEDOX®
Risk/Benefit in SAH

- Reduces mortality by almost 40% in NG IV-V
- Improves outcome
- Positive outcome despite baseline imbalances against FREEDOX
- Good safety profile
- Favorable risk/benefit ratio

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- Begin treatment within 48 hours of initial hemorrhage, preferably prior to surgery

Kaplan Meier Survival Rate
NG IV-V