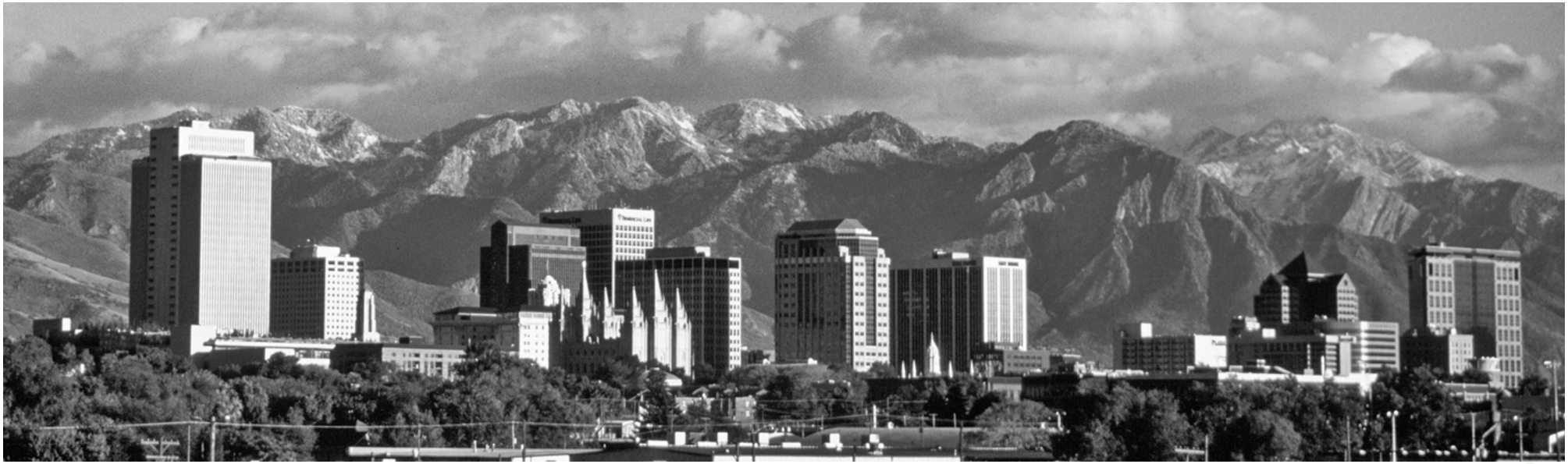
CMV Conference 2014

Salt Lake City Utah

September 26-27



CYTOMEGALOVIRUS
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UAB MEDICINE
PEDIATRICS

Children's of Alabama

Diagnosis and Treatment of Congenital Cytomegalovirus Disease

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Disclosures

- I have the following financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services.
  - Research Support from: Gilead, GlaxoSmithKline
- I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Hearing Sequelae Following Congenital CMV Infection

- CMV is the leading non-genetic cause of hearing loss in childhood
  - 1/3 of cases of sensorineural hearing loss (SNHL) due to congenital CMV
- CMV-related SNHL may be present at birth but frequently is delayed in onset
- Severity of hearing loss is variable
  - Unilateral high frequency loss to profound bilateral loss
- Progression and fluctuation of hearing loss may occur in children with CMV-related SNHL

N Engl J Med 2006;354(20):2151-64
J Am Acad Audiol 2000;11(5):283-90

Congenital CMV Infection
Characteristics of Audiologic Sequelae

Sequelae	Symptomatic	Asymptomatic
Sensorineural hearing loss	41% (85/209)	7.4% (48/651)
Characteristics of loss		
Unilateral loss	33% (28/85)	52% (25/48)
Bilateral loss	67% (57/85)	48% (23/48)
High frequency loss only	13% (11/85)	38% (18/48)
Delayed-onset loss	27% (23/85)	38% (18/48)
Progressive loss	54% (46/85)	54% (26/48)
Fluctuating loss	29% (25/85)	54% (26/48)
Improvement of loss	21% (18/85)	48% (23/48)

Dahle et al., J Am Acad Audiol 2000;11:283-290

Cumulative Percentage of Sensorineural Hearing Loss by Age

Age	Symptomatic	Asymptomatic
Birth – 1 month	43.5%	25.5%
3 months	55.3%	31.4%
6 months	67.2%	43.1%
2 years	82.4%	47.1%
3 years	88.2%	58.8%
4 years	89.4%	72.5%
6 years	95.3%	86.6%
7 – 15 years	100%	100%

Dahle et al., J Am Acad Audiol 2000;11:283-290

Congenital CMV Infection
Symptomatic Neonates

Abnormality	Positive/Total Examined (%)
Prematurity (< 38 wks)	36/106 (34)
Small for Gestational Age	53/106 (50)
Reticuloendothelial	
Petechiae	80/106 (76)
Jaundice	69/103 (67)
Hepatosplenomegaly	63/105 (60)
Purpura	14/105 (13)

Pediatr Infect Dis J 1992;11:93-9

Congenital CMV Infection
Symptomatic Neonates

Abnormality	Positive/Total Examined (%)
Neurologic	
One or more of the following:	**72/106 (68)**
Microcephaly	**54/102 (53)**
Lethargy/hypotonia	**28/104 (27)**
Poor suck	**20/103 (19)**
Seizures	**7/105 (7)**

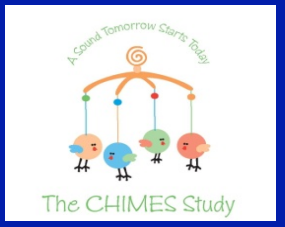
Pediatr Infect Dis J 1992;11:93-9

Congenital CMV Infection
Symptomatic Neonates

Abnormality	Positive/Total Examined (%)
Elevated ALT (> 80 units/liter)	46/58 (83)
Thrombocytopenia	
< 100 x 10^3/mm^3	62/81 (77)
< 50 x 10^3/mm^3	43/81 (53)
Conjugated hyperbilirubinemia	
Direct > 2 mg/dL	55/68 (81)
Direct > 4 mg/dL	47/68 (69)
Hemolysis	37/72 (51)
Increased CSF protein (> 120 mg/dL)	24/52 (46)

Pediatr Infect Dis J 1992;11:93-9

Comparison of Saliva and DBS for Newborn PCR Screening

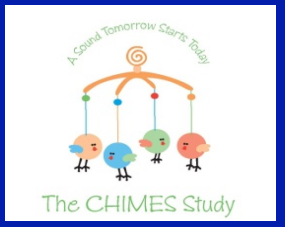


Saliva Rapid Culture	DBS PCR		Total
	Positive	Negative	
Positive	27	64	91
Negative	1	20328	20329
Total	28	20392	20420

Total positive: 92 (saliva, DBS or both)

Boppana et al., JAMA 2010;303(14):1375-1382

Comparison of Saliva and DBS for Newborn PCR Screening



- Sensitivity: 30.4% (21.5–41.0)
- Specificity: 99.9% (99.9–100)
- PPV: 84.8% (67.3–94.3)

Boppana et al., JAMA 2010;303(14):1375-1382

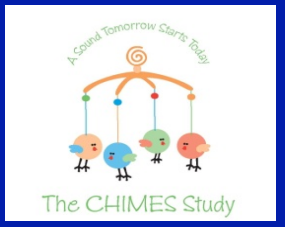
Saliva Rapid Culture vs. Liquid Saliva PCR

Saliva Rapid Culture	Liquid Saliva PCR		Total
	Positive	Negative	
Positive	85	0	85
Negative	8	17,569	17,577
Total	93	17,569	17,662

Total positive: 93 (rapid culture, PCR, or both)

Boppana et al., N Engl J Med 2011;364:2111-2118

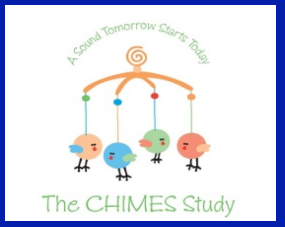
Saliva Rapid Culture vs. Liquid Saliva PCR



- Sensitivity: 100% (95.8 - 100)
- Specificity: 99.9% (99.8 - 99.9)
- PPV: 91.4% (83.8 - 96.2)
- NPV: 99.6% (99.5 - 99.7)

Boppana et al., N Engl J Med 2011;364:2111-2118

Saliva Rapid Culture vs. Dried Saliva PCR

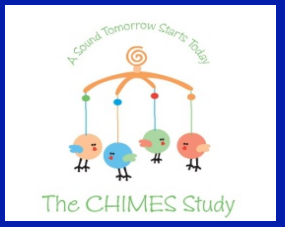


Saliva Rapid Culture	Dried Saliva PCR		Total
	Positive	Negative	
Positive	68	2	70
Negative	2	17,232	17,234
Total	70	17,234	17,304

Total positive: 70 (Rapid culture 68, PCR 68)

Boppana et al., N Engl J Med 2011;364:2111-2118

Saliva Rapid Culture vs. Dried Saliva PCR



- Sensitivity: 97.1% (90.1 - 100)
- Specificity: 99.9% (99.8 - 100)
- PPV: 94.4% (86.4 - 98.5)
- NPV: 99.9% (99.9 - 100)

Boppana et al., N Engl J Med 2011;364:2111-2118

Therapy of Congenital Cytomegalovirus Infection

- Antiviral agents with activity against CMV
  - Ganciclovir / Valganciclovir
  - Foscarnet
  - Cidofovir
  - Brincidofovir (CMX001, Chimerix, experimental)
  - Maribavir (ViroPharma, experimental)
  - Letermovir (AIC246, AiCuris/Merck, experimental)
  - Cyclopropavir (Microbiotix, experimental)

Ganciclovir / Valganciclovir

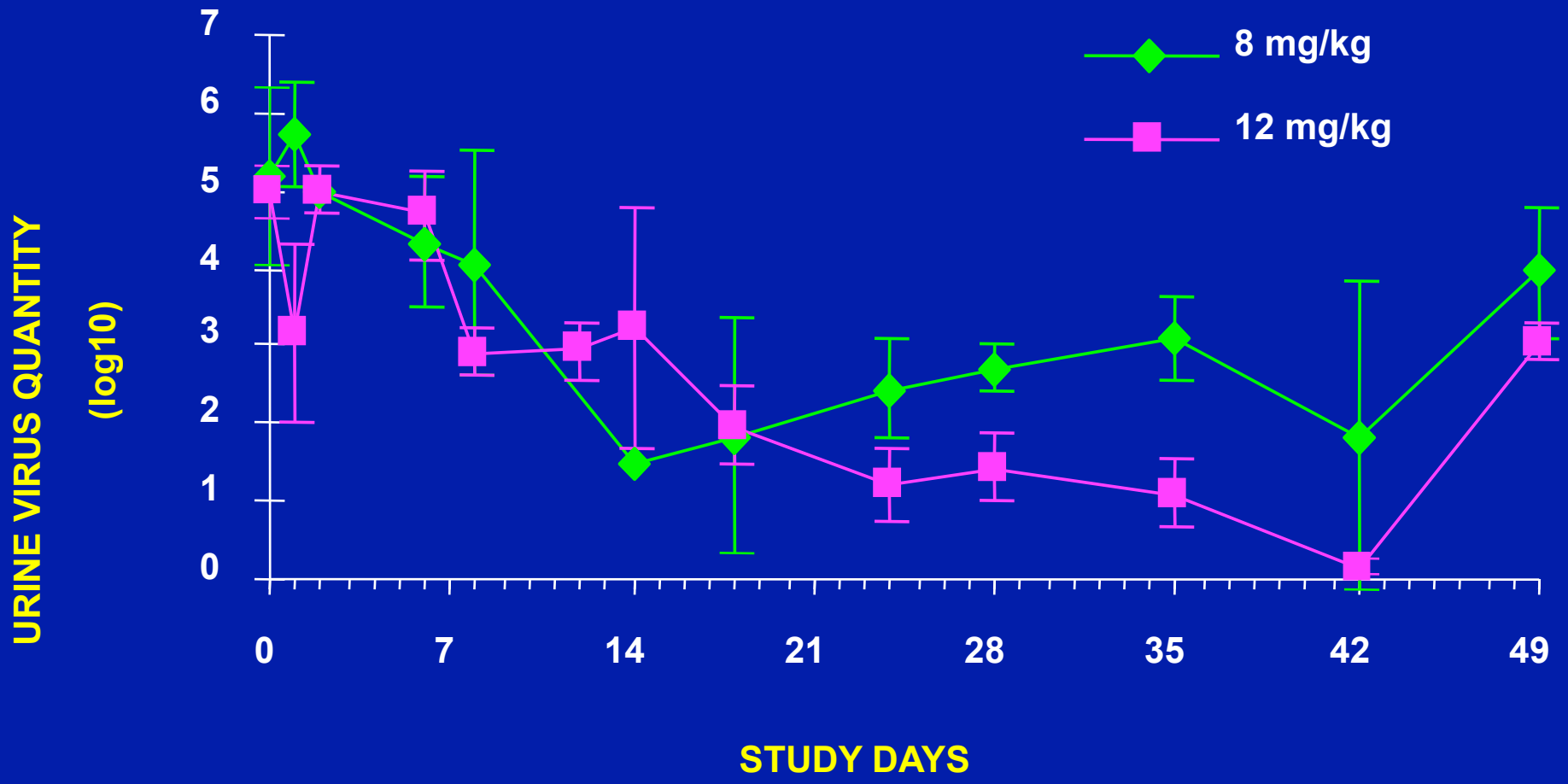
- Known toxicities
  - Bone marrow suppression
  - Neutropenia
- Potential toxicities
  - Carcinogenic in animal models
  - Gonadotoxic in animal models

Phase II Dose-Determining Investigation of Ganciclovir in Infants with Symptomatic Congenital CMV Infection

NIAID Collaborative Antiviral Study Group

J Infect Dis 1997;175:1080-86

CASG Phase II Ganciclovir Study
Virologic Response



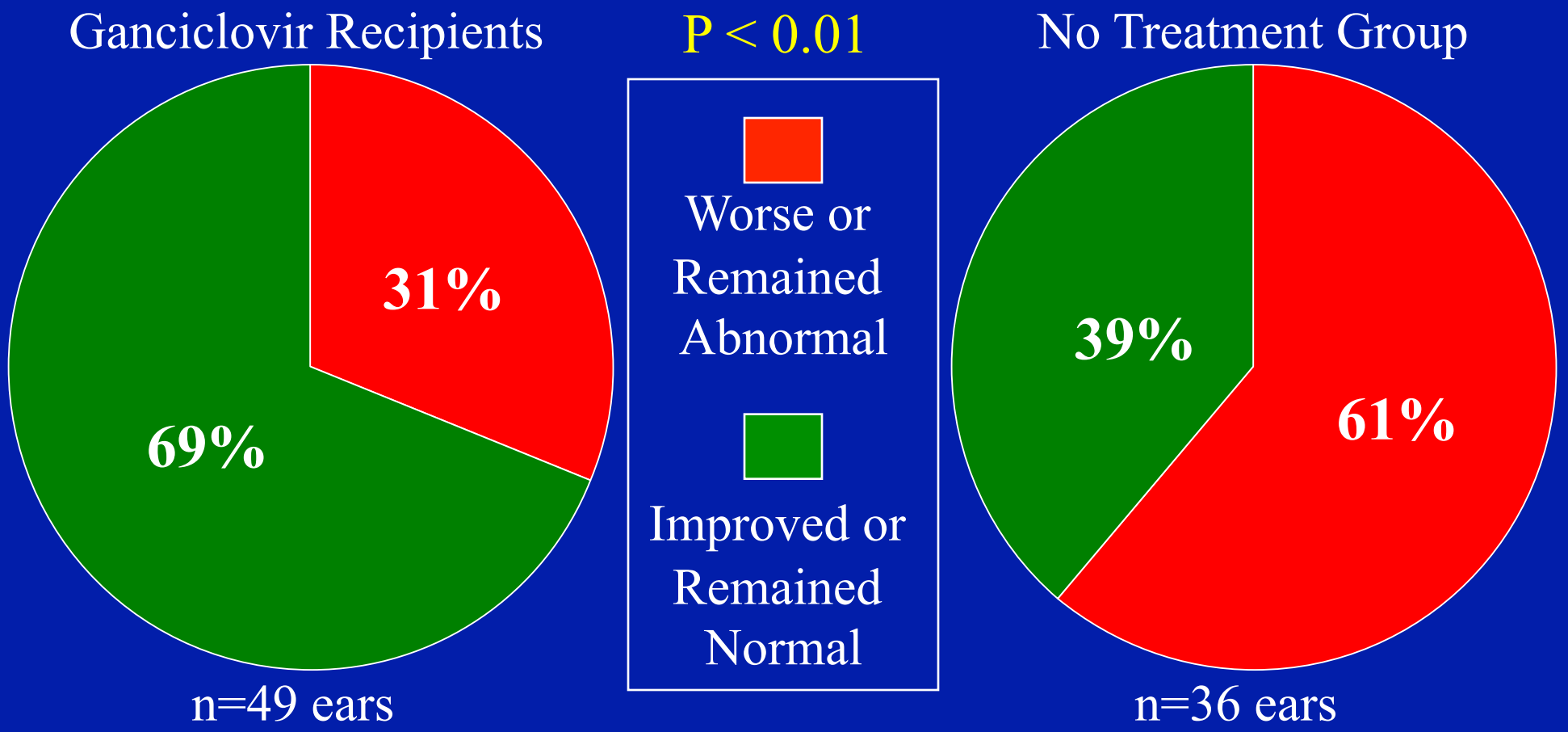
J Infect Dis 1997;175:1080-86

Phase III Randomized Controlled Investigation of the Effect of Ganciclovir On Hearing In Symptomatic Congenital Cytomegalovirus Disease

NIAID Collaborative Antiviral Study Group

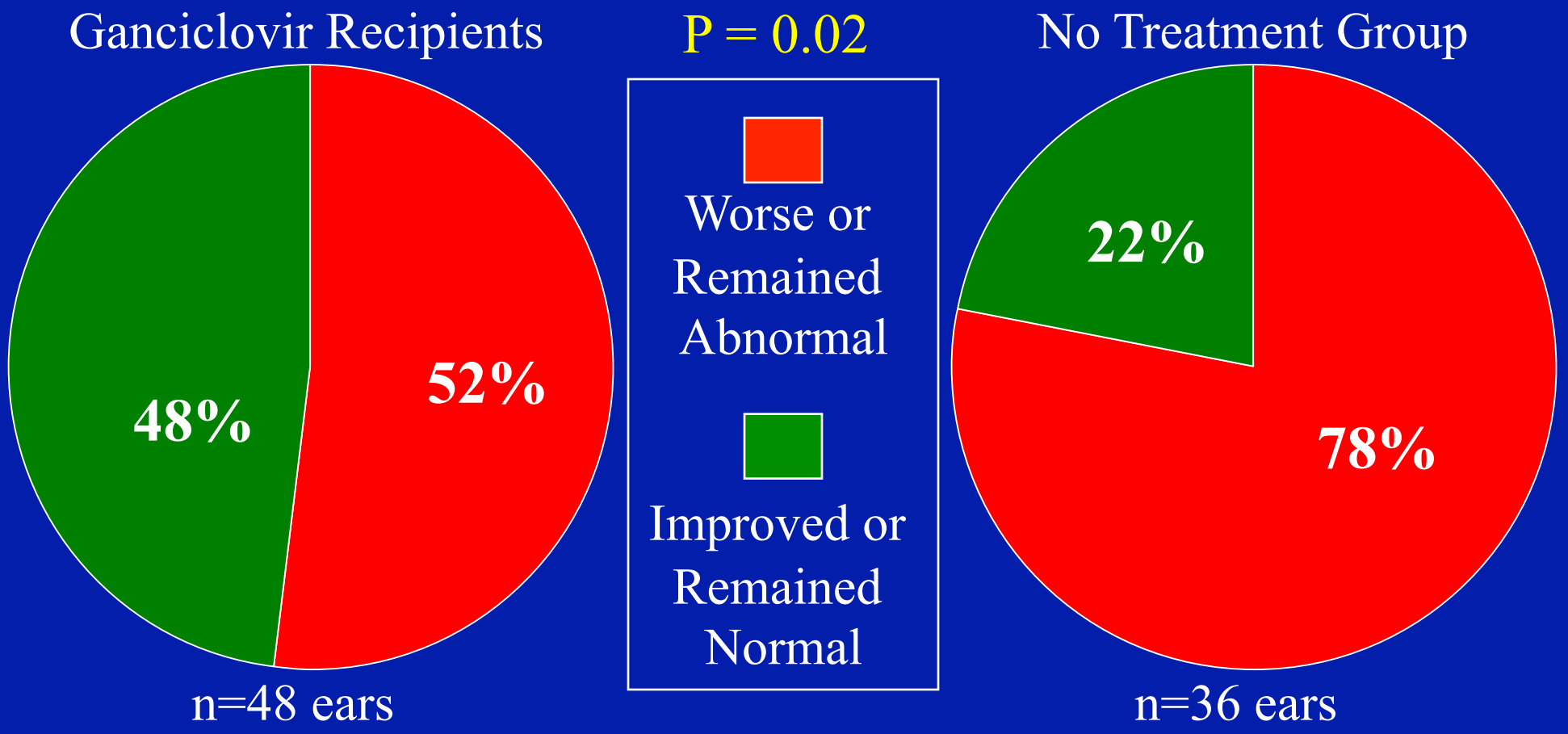
J Pediatr 2003;143:16-25

CASG Phase III Ganciclovir Study
Change in Hearing Between Birth and 6 Mos.



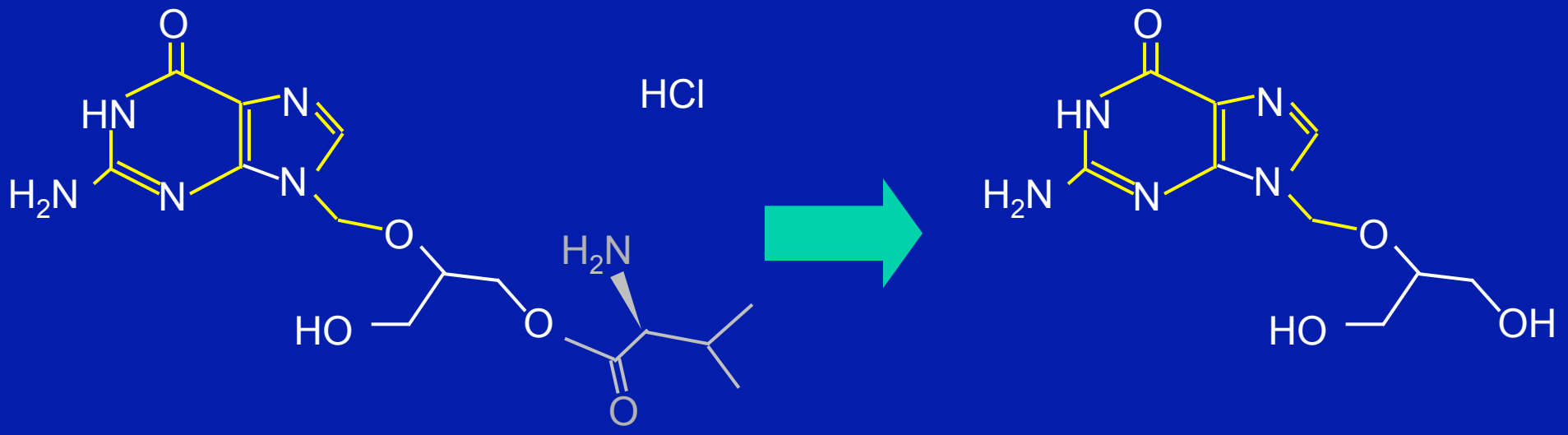
OR (95% CI): 9.96 (2.05,48.45) **J Pediatr 2003;143:16-25**

CASG Phase III Ganciclovir Study
Change in Hearing Between Birth and ≥ 1 Yr.



OR (95% CI): 4.25 (1.25,14.44) **J Pediatr 2003;143:16-25**

Valganciclovir
Pro-Drug of Ganciclovir



CASG 109: 6 Weeks Oral Valganciclovir PK/PD Study

16 mg/kg/DOSE of oral valganciclovir provides the same systemic exposure to ganciclovir as does 6 mg/kg/DOSE of IV ganciclovir

J Infect Dis 2008;197:836-845
Clin Pharmacol Therapeut 2007;81:867-872

A Phase III, Randomized, Placebo-Controlled, Blinded Investigation of Six Weeks vs. Six Months of Oral Valganciclovir Therapy in Infants with Symptomatic Congenital Cytomegalovirus Infection

CASG 112

CASG 112: 6 Wk v. 6 Mo PO Valganciclovir Study Objectives

- To compare the impact on hearing outcomes of six weeks versus six months of antiviral treatment with valganciclovir oral solution in infants with symptomatic congenital CMV disease
- To compare the impact on neurologic outcomes of six weeks versus six months of antiviral treatment with valganciclovir oral solution in infants with symptomatic congenital CMV disease
- To compare the safety profile of six weeks versus six months of antiviral therapy with valganciclovir oral solution in infants with symptomatic congenital CMV disease
- To correlate change in whole blood viral load with hearing and neurologic outcomes

CASG 112: 6 Wk v. 6 Mo PO Valganciclovir Inclusion Criteria

- Confirmation of CMV from urine or throat swab specimens by culture, shell vial, or PCR tests
- Symptomatic congenital CMV disease, as manifest by one or more of the following:
  - Thrombocytopenia
  - Petechiae
  - Hepatomegaly
  - Splenomegaly
  - Intrauterine growth restriction
  - Hepatitis (elevated transaminases and/or bilirubin)
  - Central nervous system involvement of the CMV disease (such as microcephaly, radiographic abnormalities indicative of CMV CNS disease, abnormal CSF indices for age, chorioretinitis, hearing deficits as detected by brainstem evoked response, and/or positive CMV PCR from CSF)
- ≤ 30 days of age at study enrollment
- Weight at study enrollment ≥ 1800 grams
- Gestational age ≥ 32 weeks

CASG 112: 6 Wk v. 6 Mo PO Valganciclovir Sample Size Requirements

- Power 85%
- Type I 2-sided error of 5%
- 74 evaluable subjects (37 per group)
- Expectations:
  - 15% not eligible for randomization at 6 weeks
  - Another 10% fail to complete the 6 month hearing evaluation
  - Another 10% with inadequate baseline or 6 month hearing data to adequately assess change over that time
- Total of 104 subjects targeted for enrollment
  - A 5% over-enrollment allowed for operational reasons

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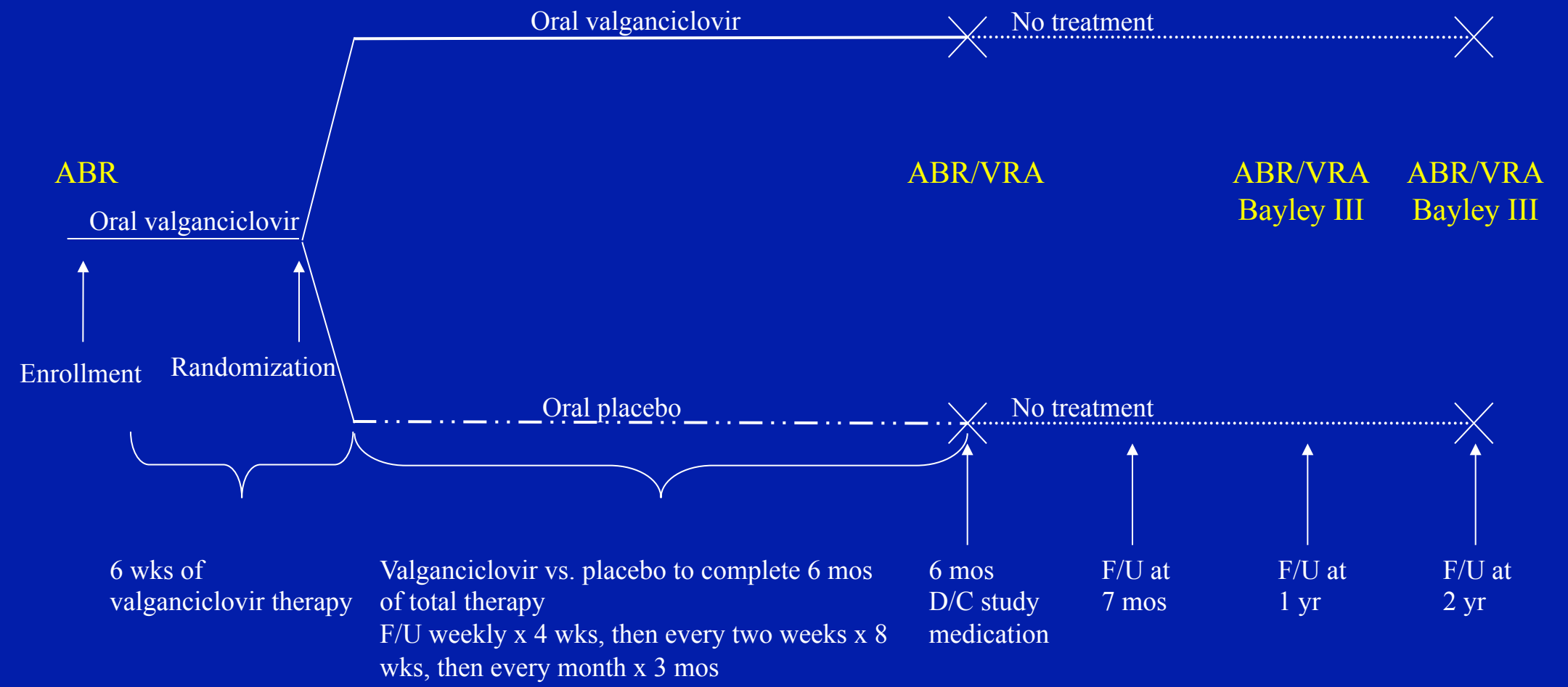
CASG 112: 6 Wk v. 6 Mo PO Valganciclovir Schematic of Study Design



CASG 112: 6 Wk v. 6 Mo PO Valganciclovir Demographics

	6 Weeks of Therapy	6 Months of Therapy	P-value
Preterm (32 to 37 wks)	22 (44.9%)	24 (51.1%)	0.68
Birth Weight (Mean ± SE)	2508.1 ± 82.7	2558.3 ± 90.2	0.95
Age at Enrollment < 14 days 15-30 days	 19 (38.8%) 30 (61.2%)	 25 (53.2%) 22 (46.8%)	0.08
Thrombocytopenia	34 (69.4%)	38 (80.8%)	0.24
Petechiae	20 (40.8%)	22 (46.8%)	0.68
Hepatomegaly	21 (42.9%)	26 (55.3%)	0.31
Splenomegaly	22 (44.9%)	23 (48.9%)	0.84
IUGR	22 (44.9%)	17 (36.2%)	0.41
↑ ALT, AST, or Bili	25 (51.0%)	21 (44.7%)	0.55
CNS Involvement	29 (59.2%)	34 (72.3%)	0.20

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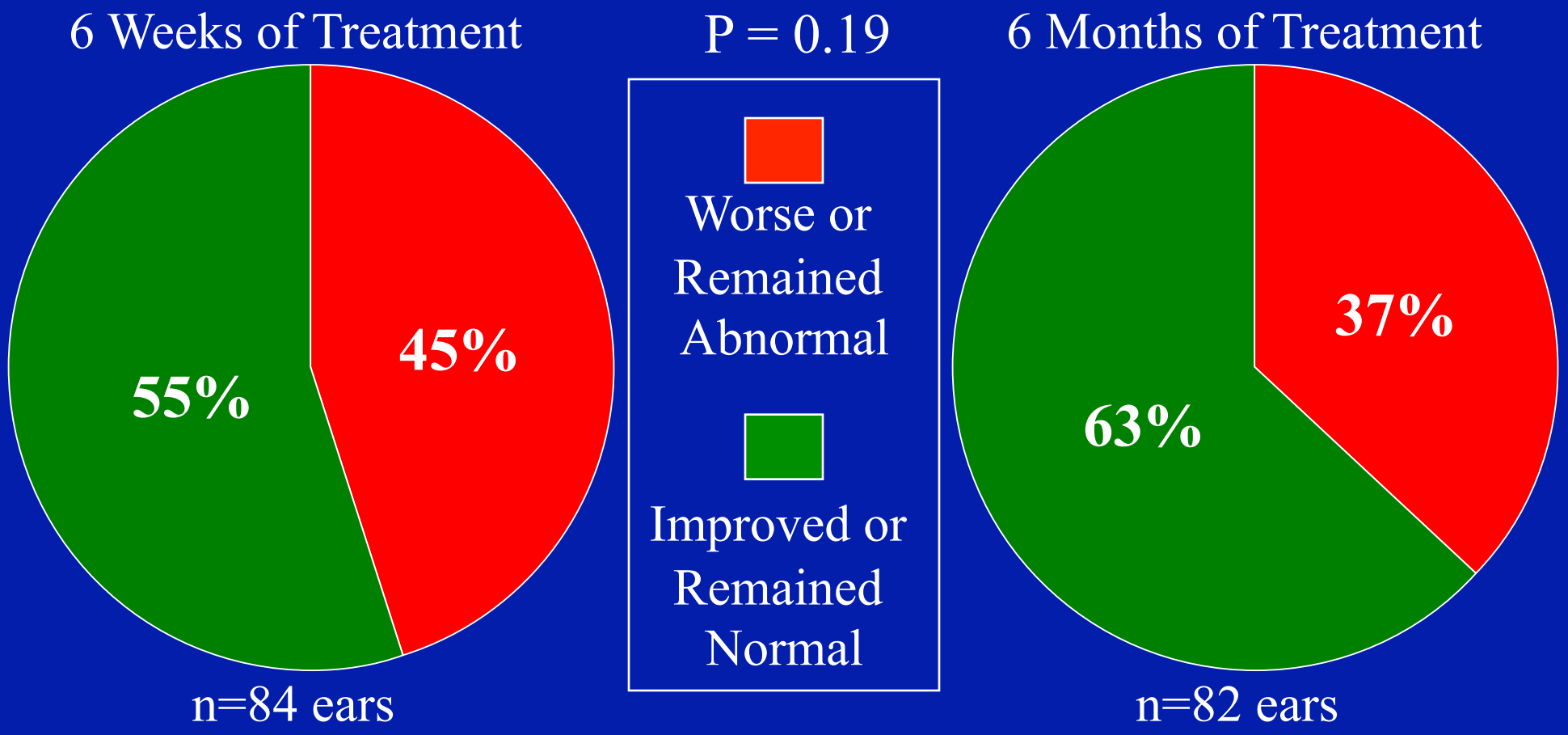
6 Weeks vs. 6 Months Oral Valganciclovir Change in Hearing Between Birth and 6 Mo



aOR (95% CI): 1.70 (0.77,3.79)

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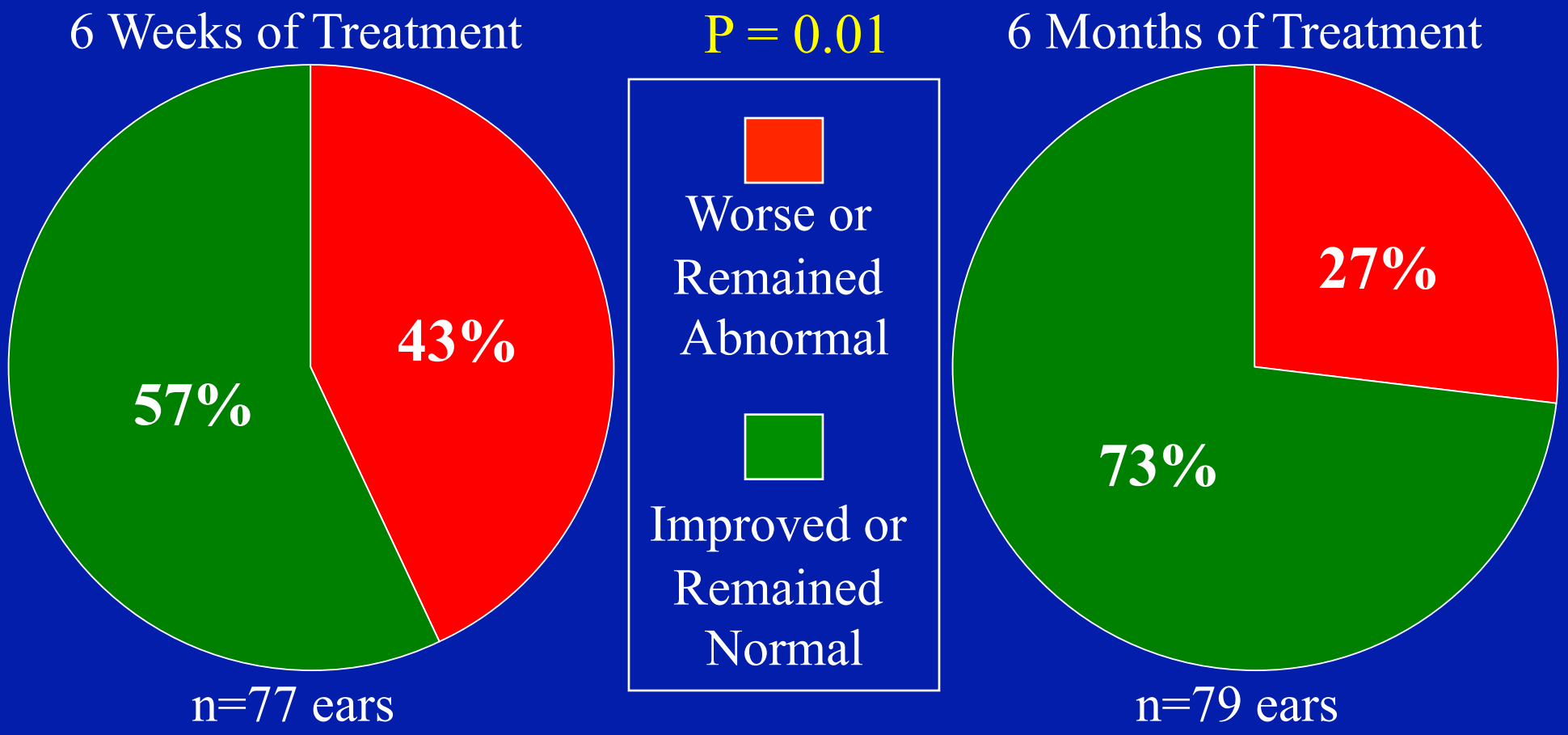
6 Weeks vs. 6 Months Oral Valganciclovir Change in Hearing Between Birth and 12 Mo



aOR (95% CI): 3.34 (1.31,8.53)

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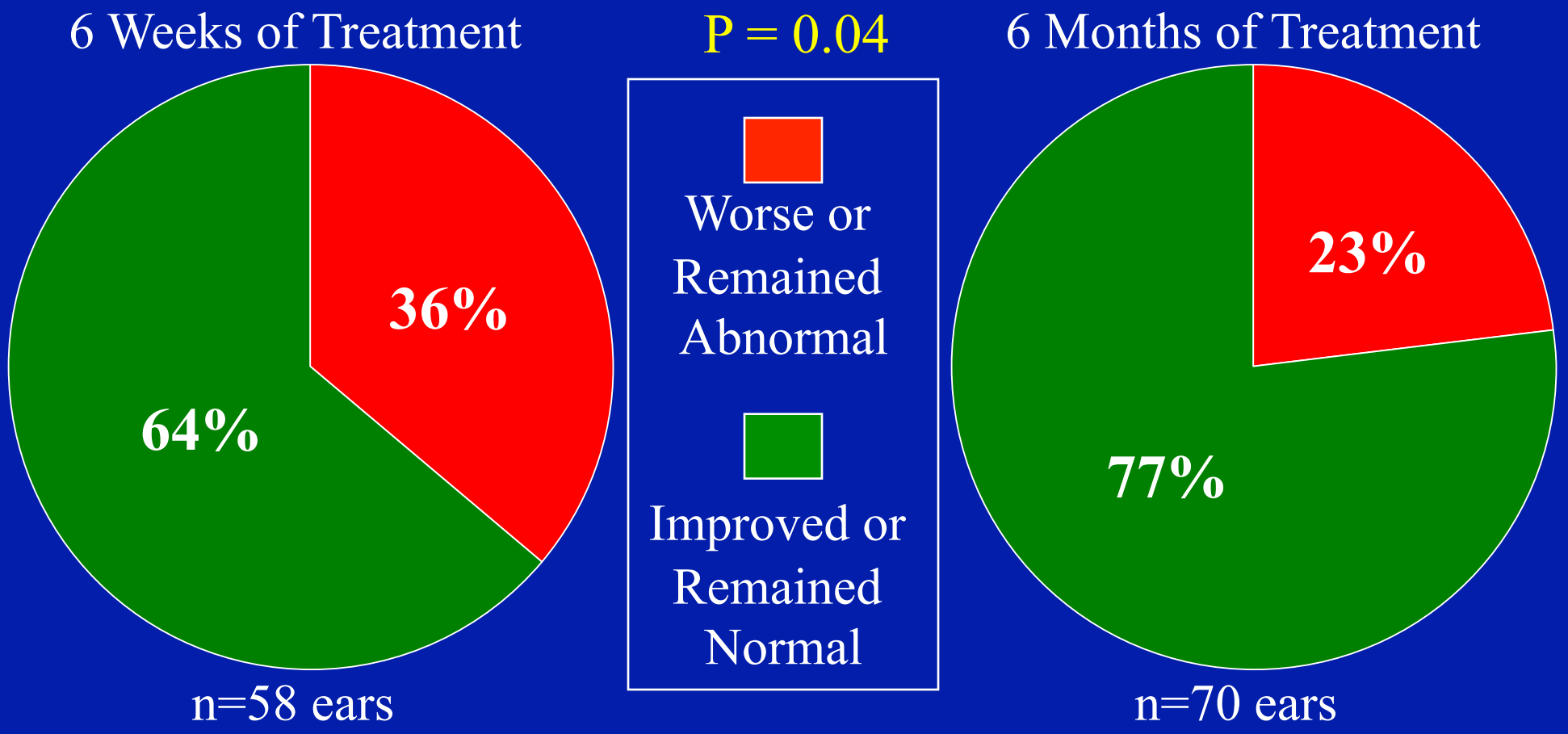
6 Weeks vs. 6 Months Oral Valganciclovir Change in Hearing Between Birth and 24 Mo



aOR (95% CI): 2.66 (1.02,6.91)

Bayley III Developmental Scale
Qualitative Descriptors of Composite Scores

Composite	Classification
130 and above	Very superior
120-129	Superior
110-119	High average
90-109	Average
80-89	Low average
70-79	Borderline
69 and below	Extremely low

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6 Weeks vs. 6 Months Oral Valganciclovir Bayley III Developmental 24 Mo Outcomes

	6 Week Therapy	6 Month Therapy	Adjusted P-value
Cognitive Composite	76.0 ± 2.6	84.4 ± 2.6	0.0236
Language Composite	72.5 ± 2.9	84.6 ± 2.9	0.0037
Receptive Communication Scale	5.2 ± 0.5	7.3 ± 0.5	0.0027
Expressive Communication Scale	5.5 ± 0.5	7.3 ± 0.5	0.0158
Motor Composite	74.1 ± 3.2	85.5 ± 3.3	0.0130
Fine Motor Scale	6.4 ± 0.6	8.0 ± 0.6	0.0566
Gross Motor Scale	5.3 ± 0.5	7.0 ± 0.5	0.0198

P-values < 0.0071 (= 0.05/7) considered statistically significant, using Bonferroni adjustment for multiple testing

Maximum Degree of Neutropenia

	Number of Subjects (% of N)					
	CASG 102		CASG 109 VGCV / GCV	CASG 112 (Day 1 – Day 42)	CASG 112 (Day 42 – Month 7)	
	No Treatment Group	GCV Group		VGCV (N=109)	Placebo (N=49)	VGCV (N=47)
Grade 3 (ANC 500-749)	8 (18.6%)	18 (39.1%)	7 (29.2%)	16 (14.7%)	8 (16.3%)*	7 (14.9%)*
Grade 4 (ANC < 500)	1 (2.3%)	11 (23.9%)	2 (8.3%)	5 (4.6%)	5 (10.2%)*	3 (6.4%)*
Total Grade 3-4	9 (20.9%)	29 (63.0%)	9 (37.5%)	21 (19.3%)	13 (26.5%)*	10 (21.3%)*

*P>0.6

Interruption of Treatment Due to Neutropenia

- 3 subjects had study drug held for ANCs < 500 cells/ mm^3
- All treatment interruptions occurred within the first 6 weeks, when all subjects were on active therapy
- Neutropenia resolved in 1 week, 2 weeks, and 3.5 months in these 3 cases
  - The 2 subjects with rapid recoveries had ANC > 500 cells/ mm^3 initially, and randomized to placebo
  - The 1 subject with slow recovery had ANC of 400 cells/ mm^3 initially, and randomized to active drug

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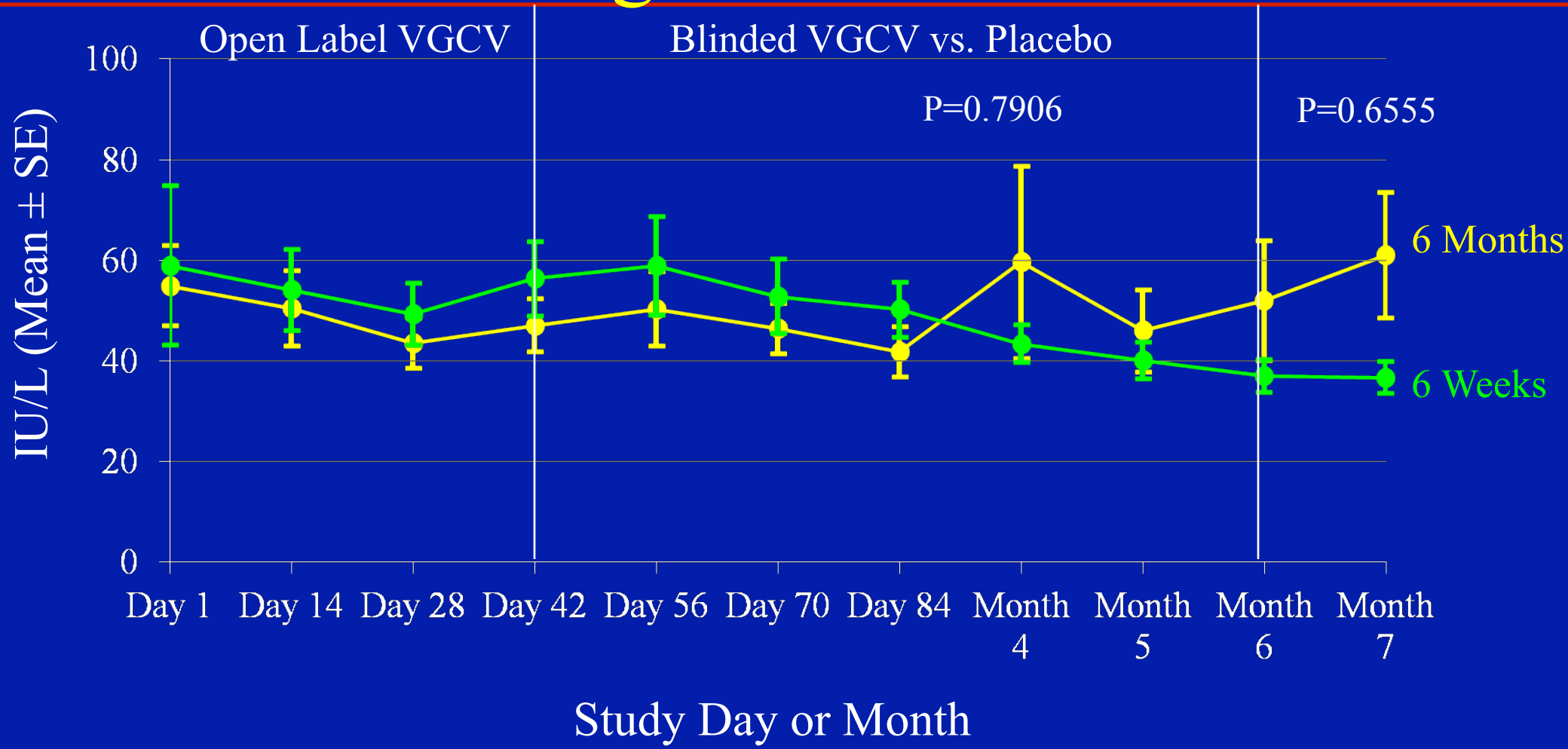
Alanine Aminotransferase (ALT) Change Over Time



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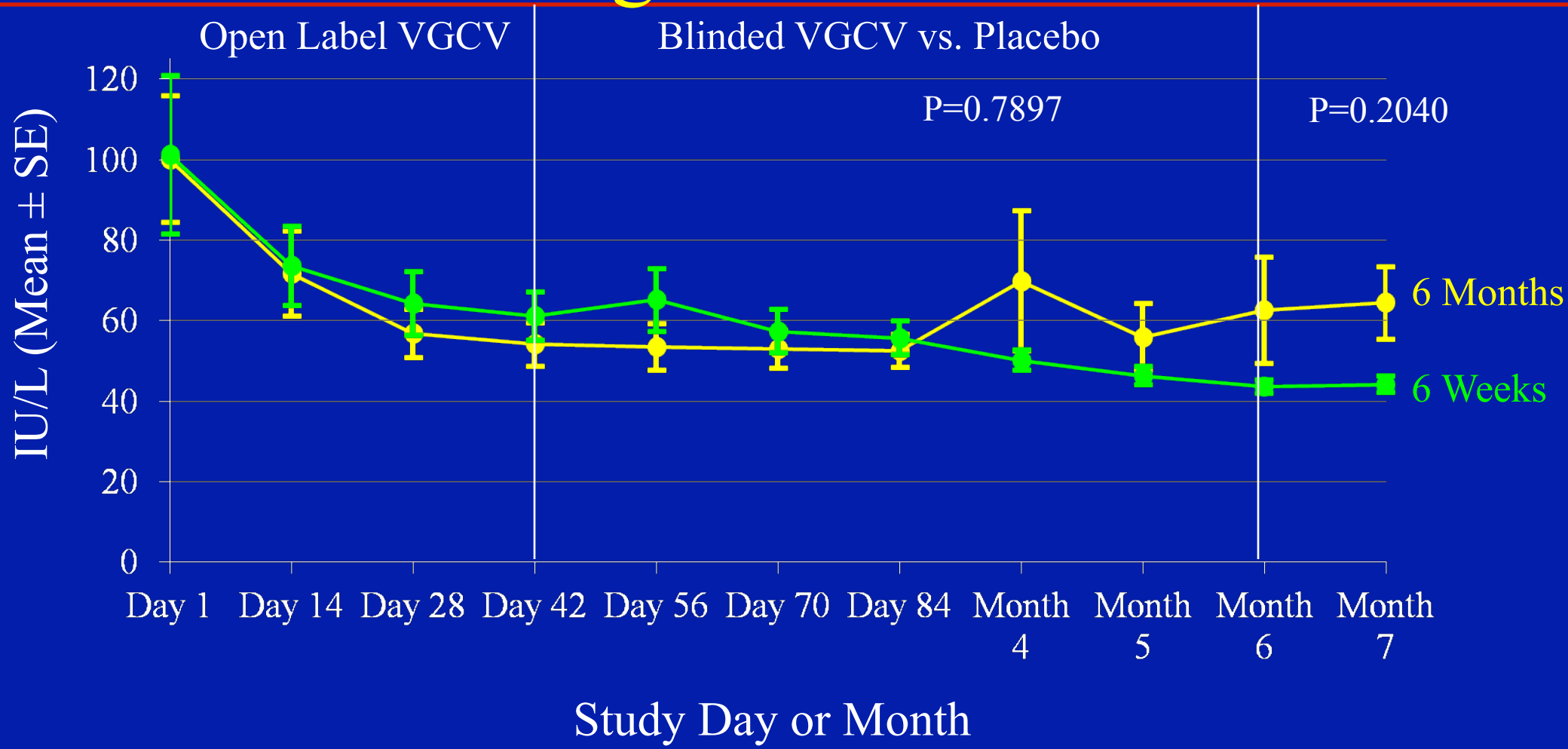
Aspartate Aminotransferase (AST) Change Over Time



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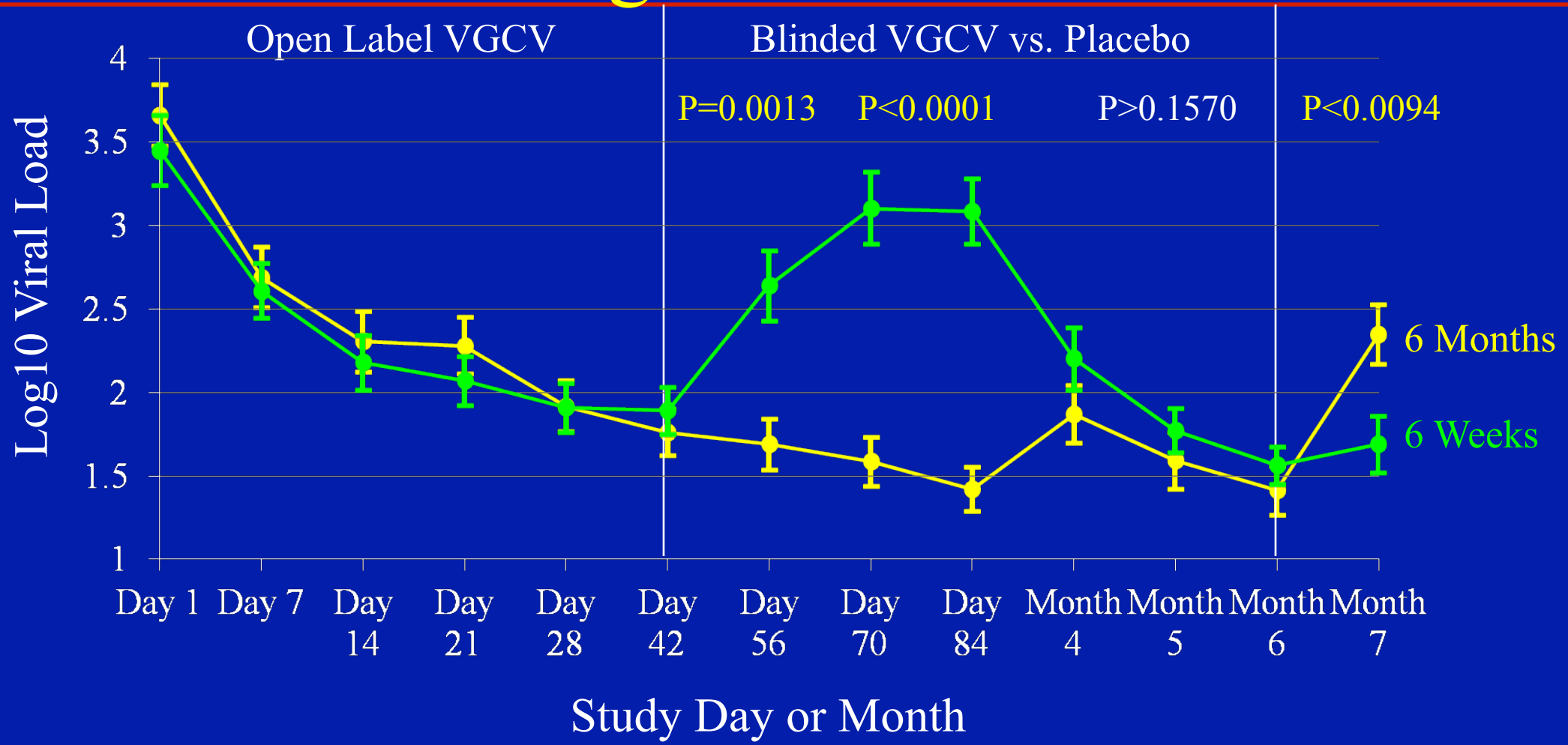
Whole Blood CMV Viral Load Change Over Time



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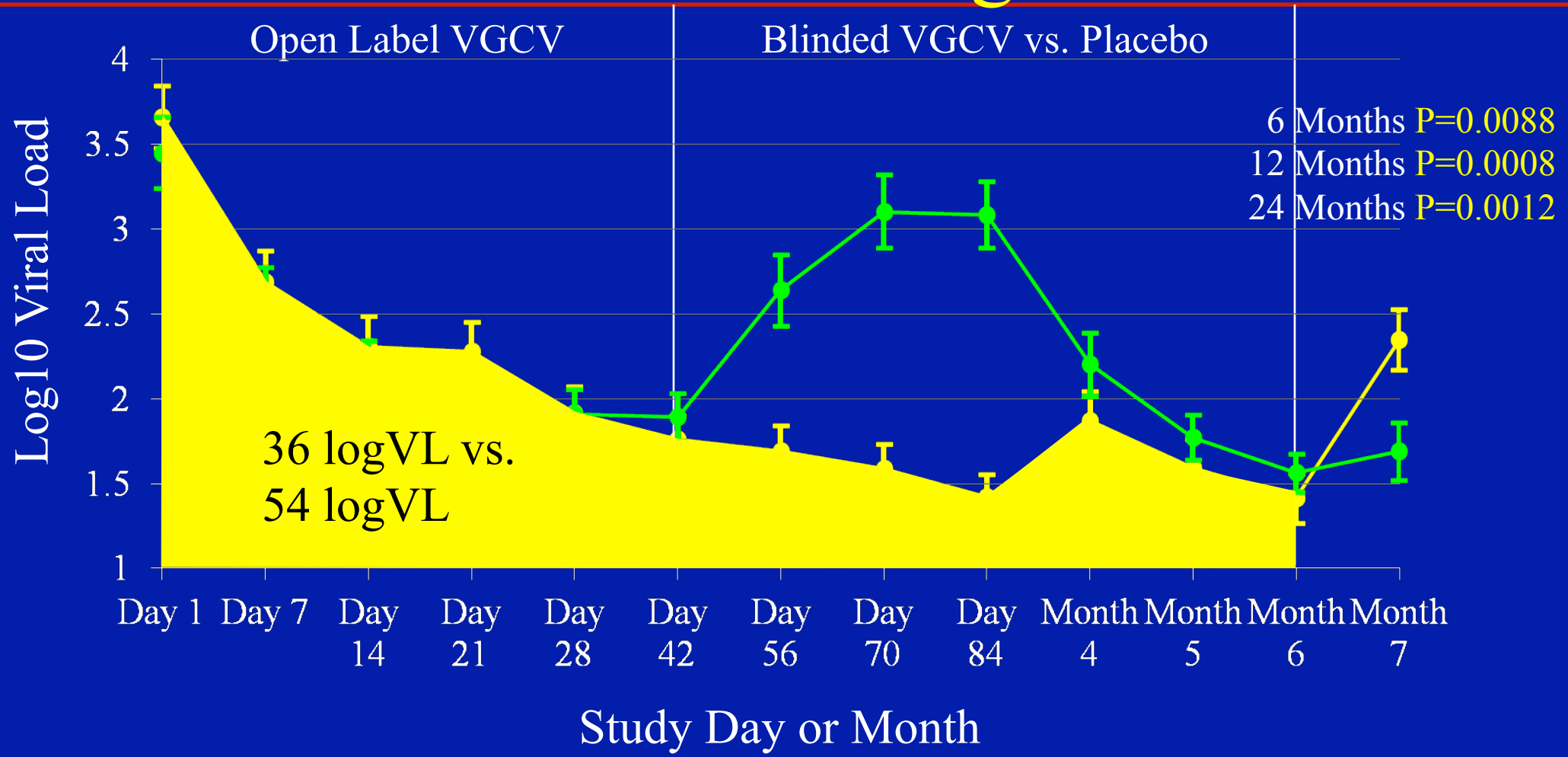
Correlation with Viral Load AUC With Hearing



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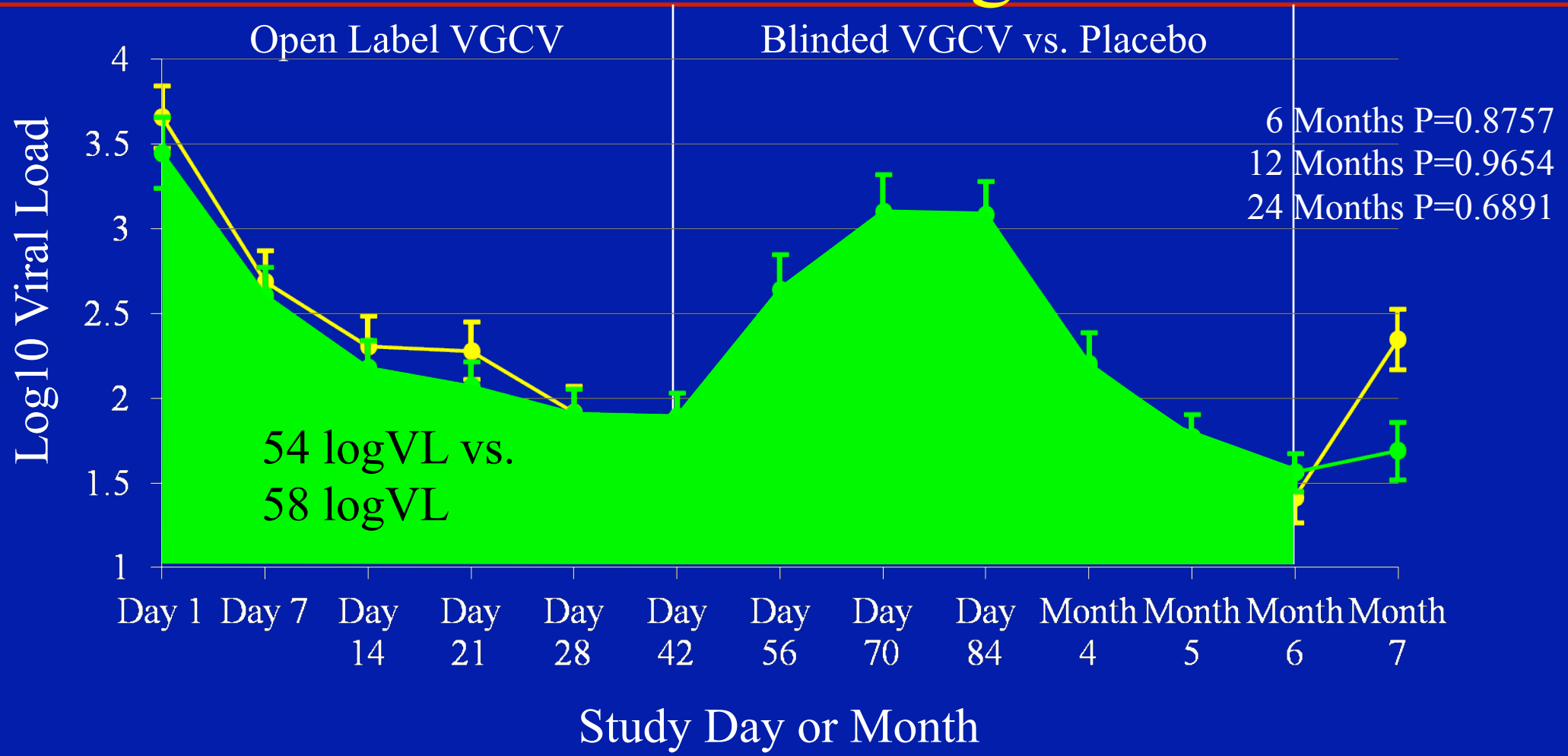

Viral Load Analyses

- Higher whole blood viral load associated with CNS involvement at baseline (mean log viral load = 3.84 ± 0.15 for CNS and 2.94 ± 0.21 for non-CNS, p=0.0005)
- Higher VL at baseline associated with worse Cognitive composite (p=0.006) and fine motor (p=0.003) neurodevelopmental outcomes at 24 months
- No correlation between viral load AUC and neurodevelopmental outcomes beyond that provided by treatment itself

CASG 112: 6 Wk v. 6 Mo PO Valganciclovir Conclusions

- Treating symptomatic congenital CMV disease with 6 months of valganciclovir, compared with 6 weeks, does not improve short-term hearing but modestly improves longer-term hearing and developmental outcomes
  - Improved audiologic outcomes at 12 and 24 months
  - Improved communicative neurodevelopmental outcomes at 24 months
- Neutropenia is less common with longer-term oral valganciclovir than with IV ganciclovir
- AST/ALT may be higher in valganciclovir group at Month 4 and 5, but it is not statistically significant

Take-Home Points

- Antiviral therapy in neonates with symptomatic congenital CMV disease with or without CNS involvement modestly improves audiologic and developmental outcomes
- Duration of treatment should now be 6 months
- Treatment should be limited to symptomatic congenital CMV disease (with or without CNS involvement)
- No controlled data exist to support treatment of babies with asymptomatic congenital CMV infection

University of Alabama at Birmingham
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