From: Pandina, Gahan [JANUS]
Sent: Wednesday, November 20, 2002 8:39 PM
To: Gharabawi, Georges [JANUS]
Subject: C&A Prolactin Data

Importance: High

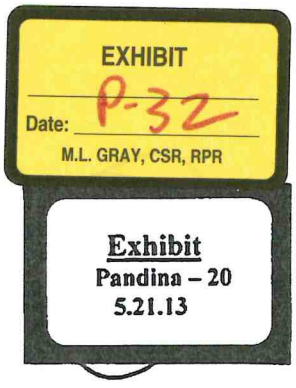
C&A.NAB.Prolactin. FINAL.ppt (3...

Georges,

Attached is the prolactin presentation (MRC reviewed) that was given at the national advisory board last week.

Gahan

Gahan J. Pandina, Ph.D.
Assistant Director, CNS Clinical Development
Janssen Pharmaceutica Products, L.P.
1125 Trenton-Harbourton Rd * Titusville, NJ 08560
OFFICE: (609) 730 2324 * FAX: (609) 730 3125
EMAIL: gpandina@janus.jnj.com



PLAINTIFF'S EXHIBIT 32

Long-term Risperidone Treatment vs Prolactin Levels

Carin Binder, MBA
Director, Clinical Affairs
Janssen-Ortho, Inc.

Questions From June Advisory Board

- How do prolactin values change over time?
- Is there as relationship between prolactin level and:
  - Duration of treatment
  - Age
  - Gender
  - Weight
  - SHAP
  - Motor effects
  - Clinical response
  - Comorbid ADHD and PSTIM

Description of Datasets and Baseline Demographics

Multicenter Studies of Risperidone Use in Children With Disruptive Behavior Disorders

Study ID	Design	Duration (weeks)
RIS-CAN-19	Double-blind, placebo-controlled	6
RIS-CAN-20*	Open-label follow-up to RIS-CAN-19	48
RIS-USA-93	Double-blind, placebo-controlled	6
RIS-USA-97*	Open-label follow-up to RIS-USA-93	48
RIS-INT-41	Separate open-label trial to collect safety data	48

* Eligibility limited to children with at least 2 weeks of treatment during the preceding double-blind trial

REFERENCES

- Aman, M., DeSmedt, G., Derivan, A., Lyons, B., Findling, R. (2002). Double-blind, placebo controlled, study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *Am J Psychiatry*, 159, 1337-1346.
- Snyder, R., Turgay, A., Aman, M., Binder, C., Fisman, S., Carroll, A. (2002). Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. *JAACAP*, 41:9, 1026-1036.
- Turgay, A., et al (2002). Long-term safety and efficacy of risperidone for the treatment of disruptive behavior disorders in children with subaverage IQs. *Pediatrics*, 110 (3), pp:e34.

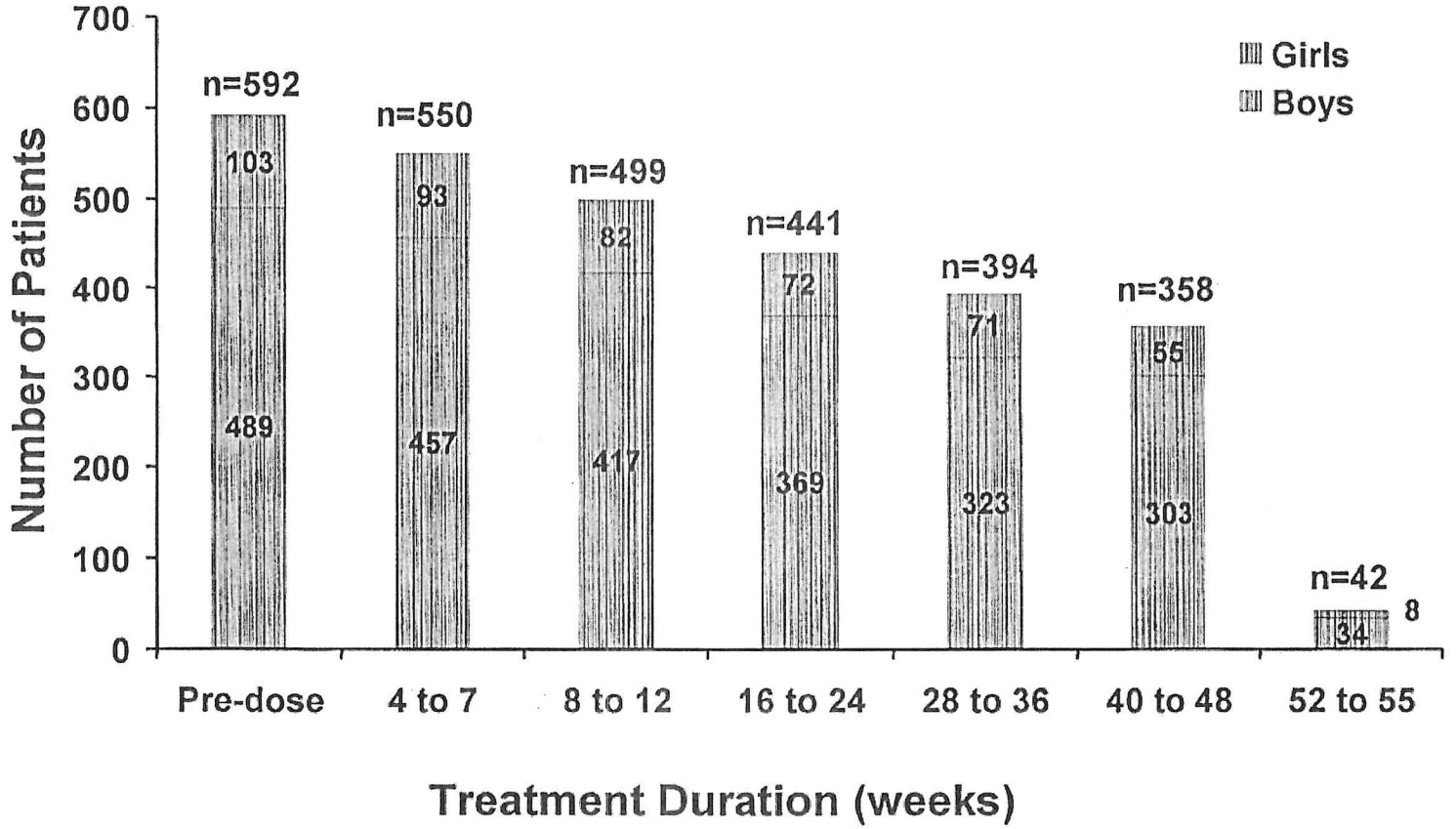
Data on file: Johnson & Johnson PRD, LLP

Analysis Populations

- ITT population
  - Patients who received at least 1 dose of risperidone
- Primary analysis population (PAP)
  - Subset of the ITT population with pre-dose and at least 1 post-dose PRL observation at or after 4 weeks

Data on file: Johnson & Johnson PRD, LLC

Number of Patients With Prolactin Measurements at Each Time Point
(PAP–as observed)



Data on file: Johnson & Johnson PRD, LLC

Patient Demographics

Characteristic	ITT Population N=700	Primary Analysis Population (PAP) N=592	Non-PAP N=108
Age, years			
Mean (±SD)	9.9 ± 2.4	9.9 ± 2.5	9.7 ± 2.3
Median (range)	9.9 (5.0–15.0)	9.9 (5.1–15.0)	9.8 (5.0–14.7)
Gender, n (%)			
Boys	574 (82.0)	489 (82.6)	85 (78.7)
Girls	126 (18.0)	103 (17.4)	23 (21.3)
Race, n (%)			
Black	78 (11.2)	57 (9.6)	21 (19.6)
White	550 (78.7)	475 (80.2)	75 (70.1)
Other	72 (10.1)	60 (10.2)	12 (11.2)

Data on file: Johnson & Johnson PRD, LLC

Pre-dose Characteristics

Characteristic	ITT Population	Primary Analysis Population (PAP)	Non-PAP
Tanner Stage, n (%)	n=700	n=592	n=108
0	6 (0.9)	4 (0.7)	2 (2.1)
1	487 (72.6)	420 (73.0)	67 (69.8)
2	96 (14.3)	83 (14.4)	13 (13.5)
3	44 (6.6)	36 (6.3)	8 (8.3)
4	29 (4.3)	23 (4.0)	6 (6.3)
5	9 (1.3)	9 (1.6)	0
NA	29	17	12
Weight, kg (±SD)	n=698 35.1 ± 13.2	n=591 35.3 ± 13.4	n=107 33.6 ± 11.7
Height, cm (±SD)	n=679 137.5 ± 15.6	n=573 137.8 ± 15.9	n=106 135.9 ± 14.3
IQ, mean (±SD)	n=699 65.1 ± 13.4	n=591 65.1 ± 13.3	n=108 65.4 ± 14.0
DSM-IV Axis II, n (%)	n=700	n=592	n=108
Borderline mental retardation	288 (41.2)	236 (39.9)	52 (48.1)
Mild mental retardation	282 (40.3)	248 (42.0)	34 (31.5)
Moderate mental retardation	129 (18.5)	107 (18.1)	22 (20.4)
NA	1	1	0

Data on file: Johnson & Johnson PRD, LLC

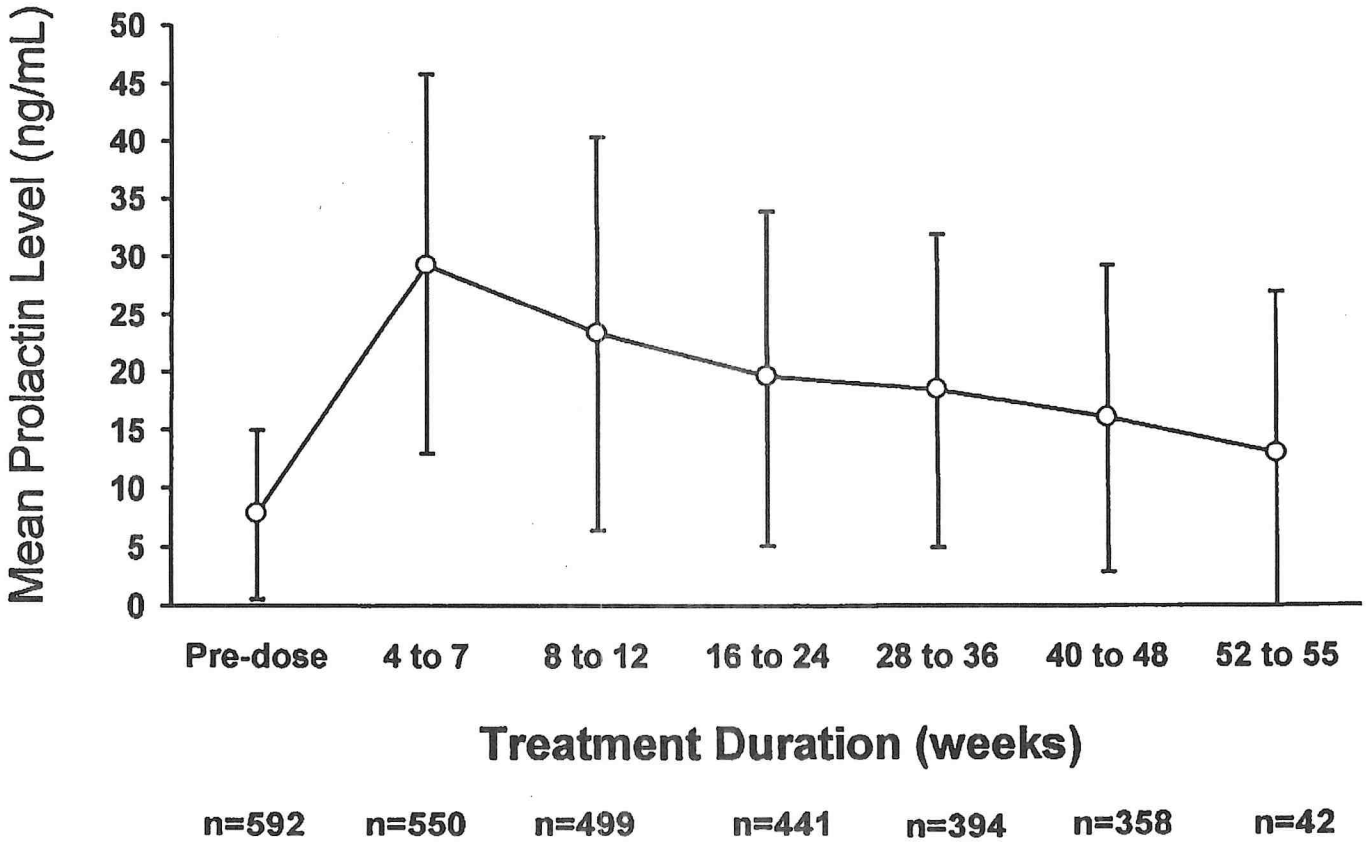
Risperidone Dosing

	ITT Population N=700	Primary Analysis Population (PAP) N=592	Non-PAP N=108
Duration of risperidone exposure (days) Mean ± SD Median (range)	 308 ± 116.1 359 (1 to 505)	 319 ± 101.3 361 (28 to 505)	 245 ± 163.4 336 (1 to 498)
Average daily dose (mg) Mean ± SD Median (range)	 1.23 ± 0.72 1.20 (0 to 4.17)	 1.26 ± 0.70 1.22 (0 to 4.17)	 1.05 ± 0.77 0.96 (0.02 to 3.48)

Data on file: Johnson & Johnson PRD, LLC

Risperidone Dose

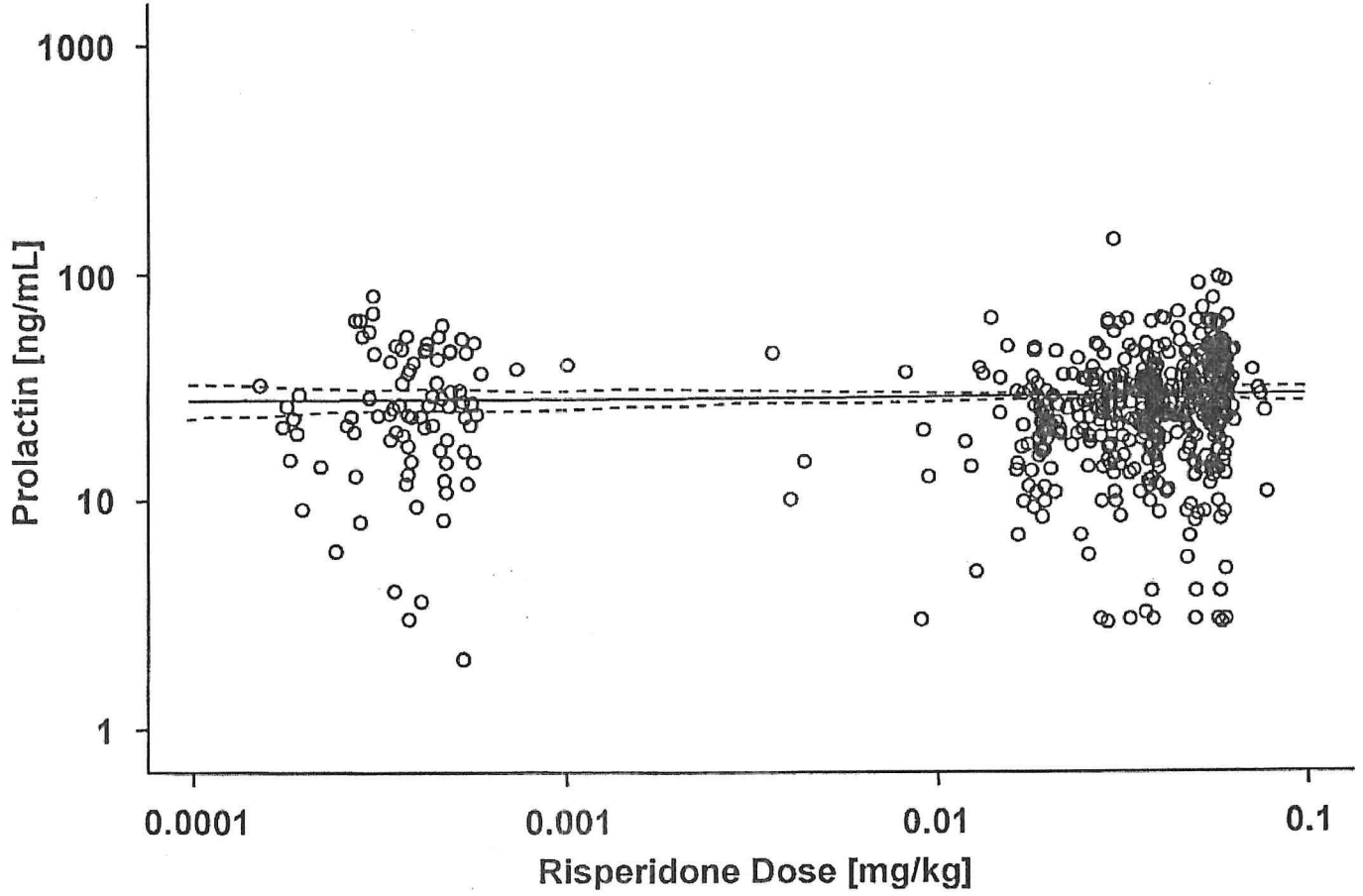
Prolactin Levels by Exposure: All Patients



Data on file: Johnson & Johnson PRD, LLC

Prolactin Levels vs Dose

Weeks 4 to 7 (PAP–as Observed): Log Scale

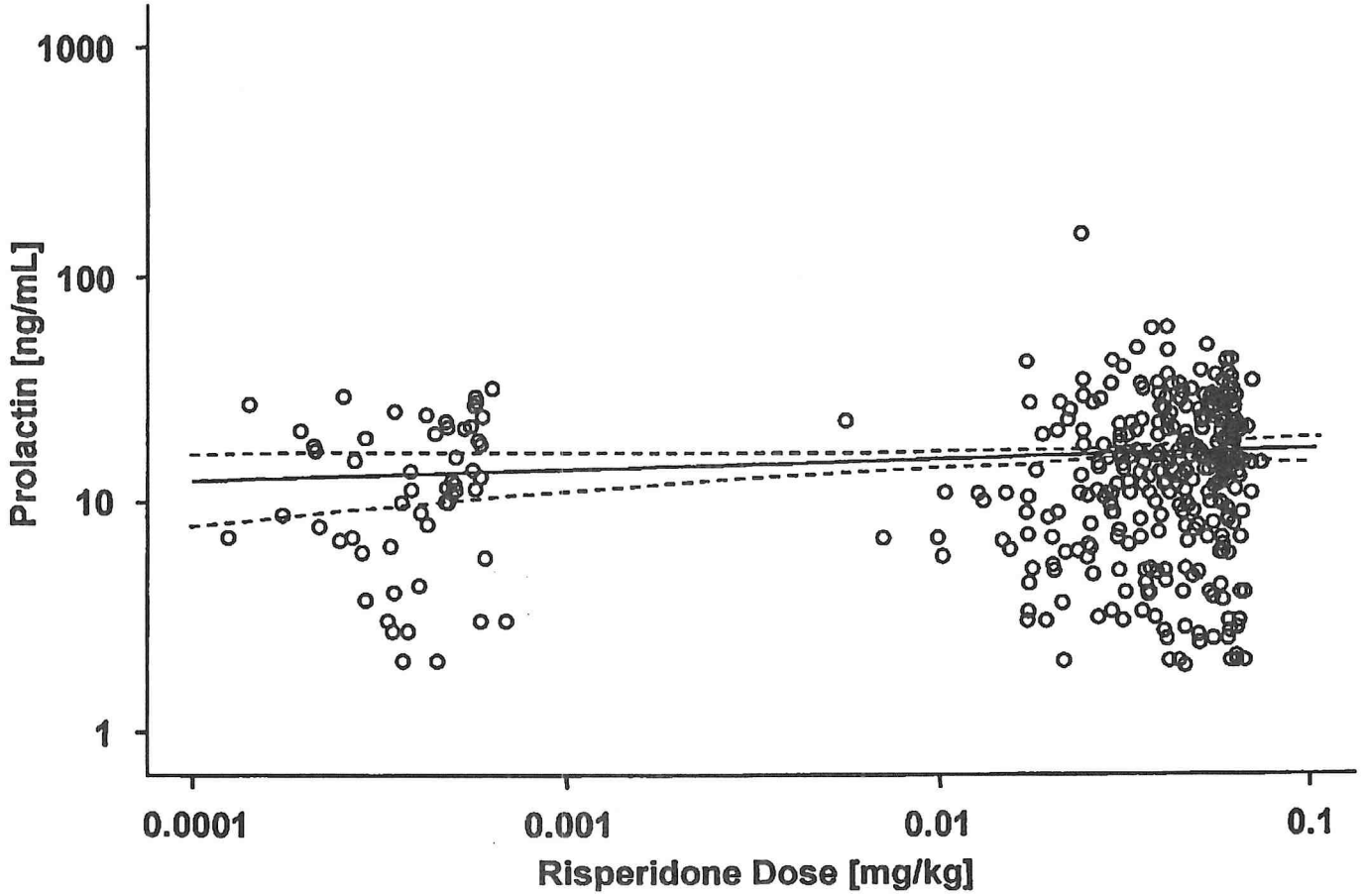


*Log scale used due to large range of individual values for PRL and risperidone dose

Data on file: Johnson & Johnson PRD, LLC

Prolactin Levels vs Dose

Weeks 40 to 48 (PAP–as Observed): Log Scale



*Log scale used due to large range of individual values for PRL and risperidone dose

Data on file: Johnson & Johnson PRD, LLC

Correlation Between Risperidone Dose and PRL Level

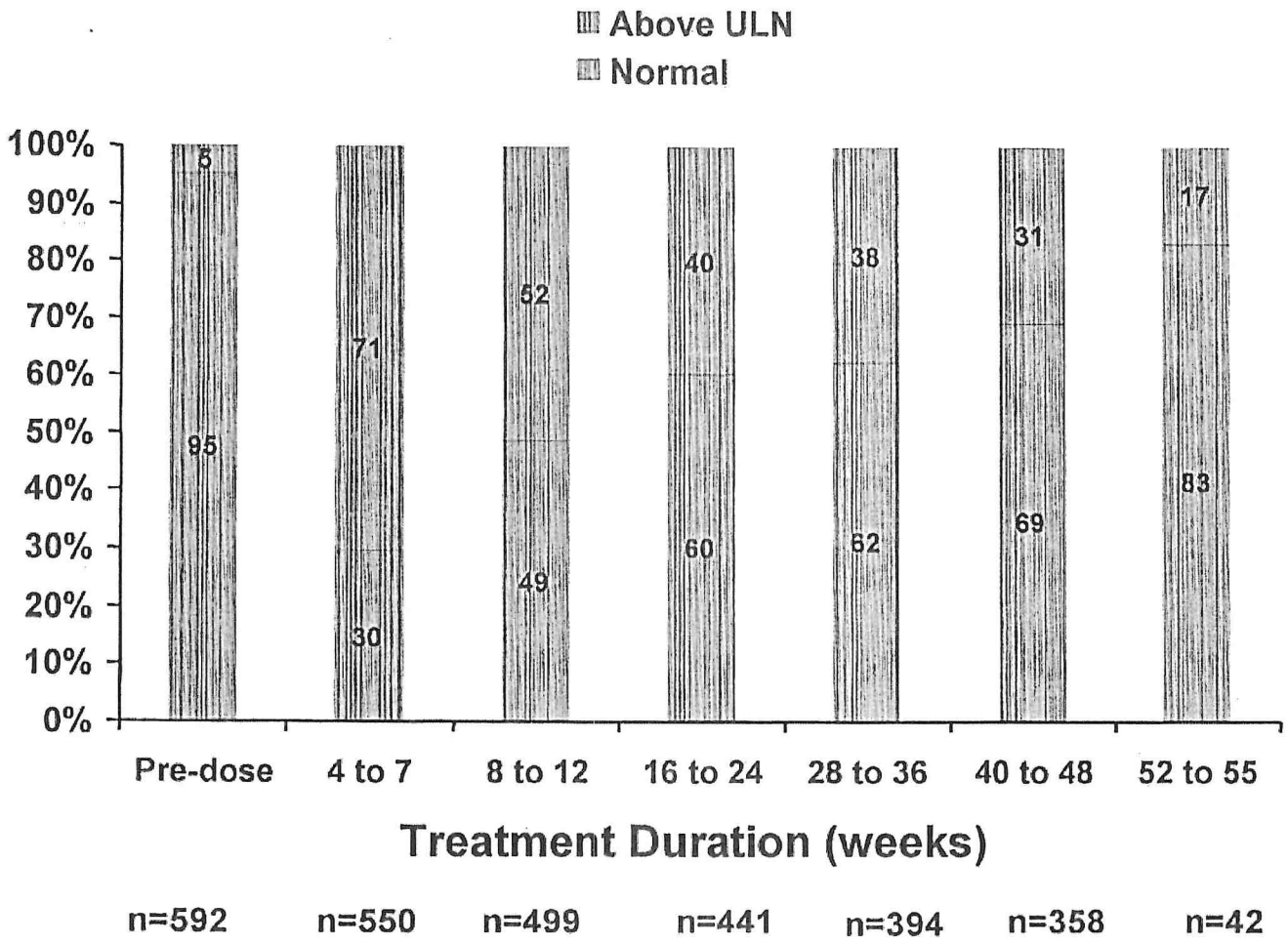
Treatment Duration (weeks)	n	Variance (Percent)*
Weeks 4 to 7	550	0.30
Weeks 8 to 12	499	0.01
Weeks 16 to 24	441	0.11
Weeks 28 to 36	394	0.25
Weeks 40 to 48	358	0.78

***Percent of variation in prolactin level that can be attributed to risperidone dose; R^2 x 100**

Data on file: Johnson & Johnson PRD, LLC

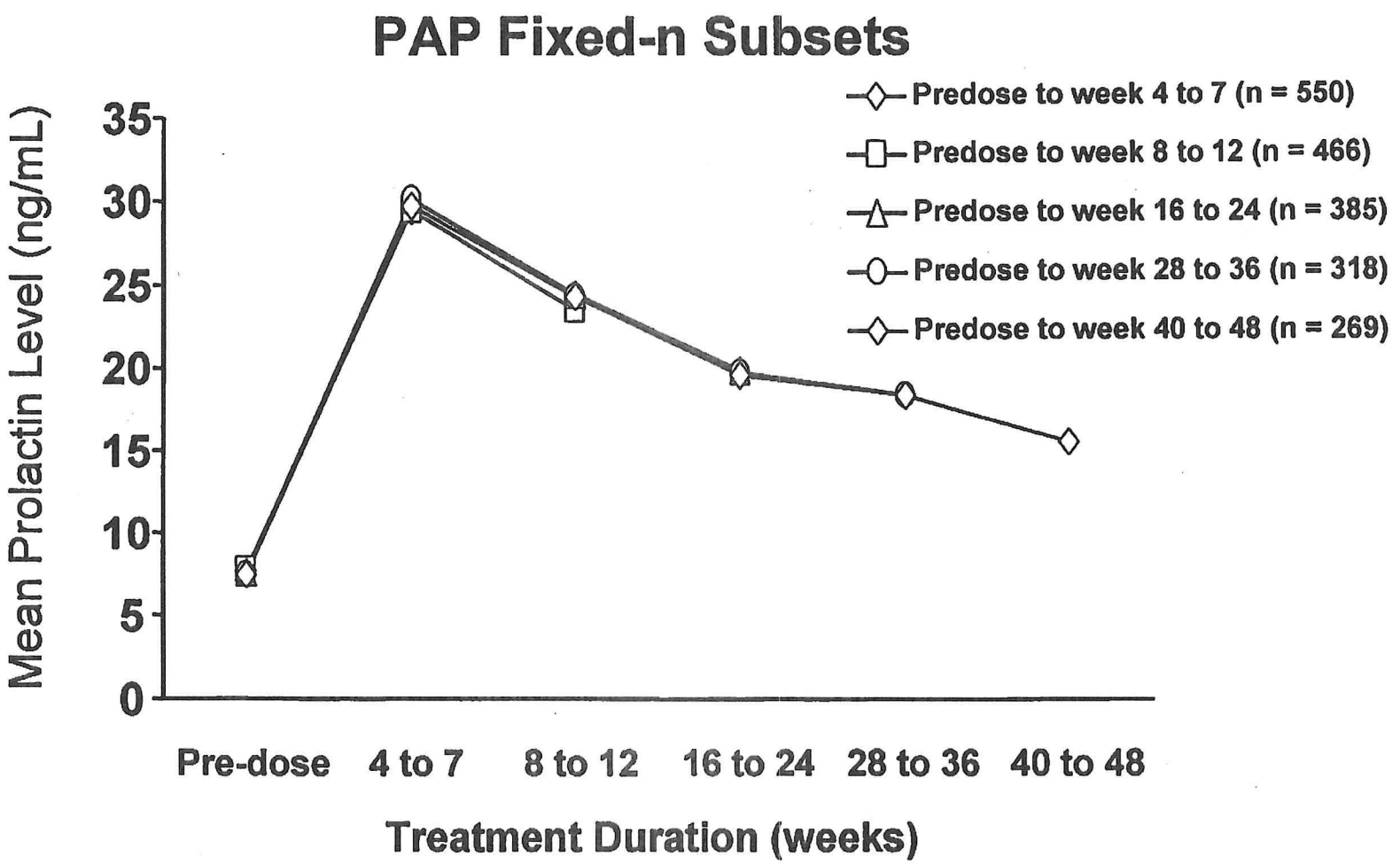
Duration of Treatment

Incidence of Prolactin Levels: Normal and Above Upper Limit of Normal



Data on file: Johnson & Johnson PRD, LLC

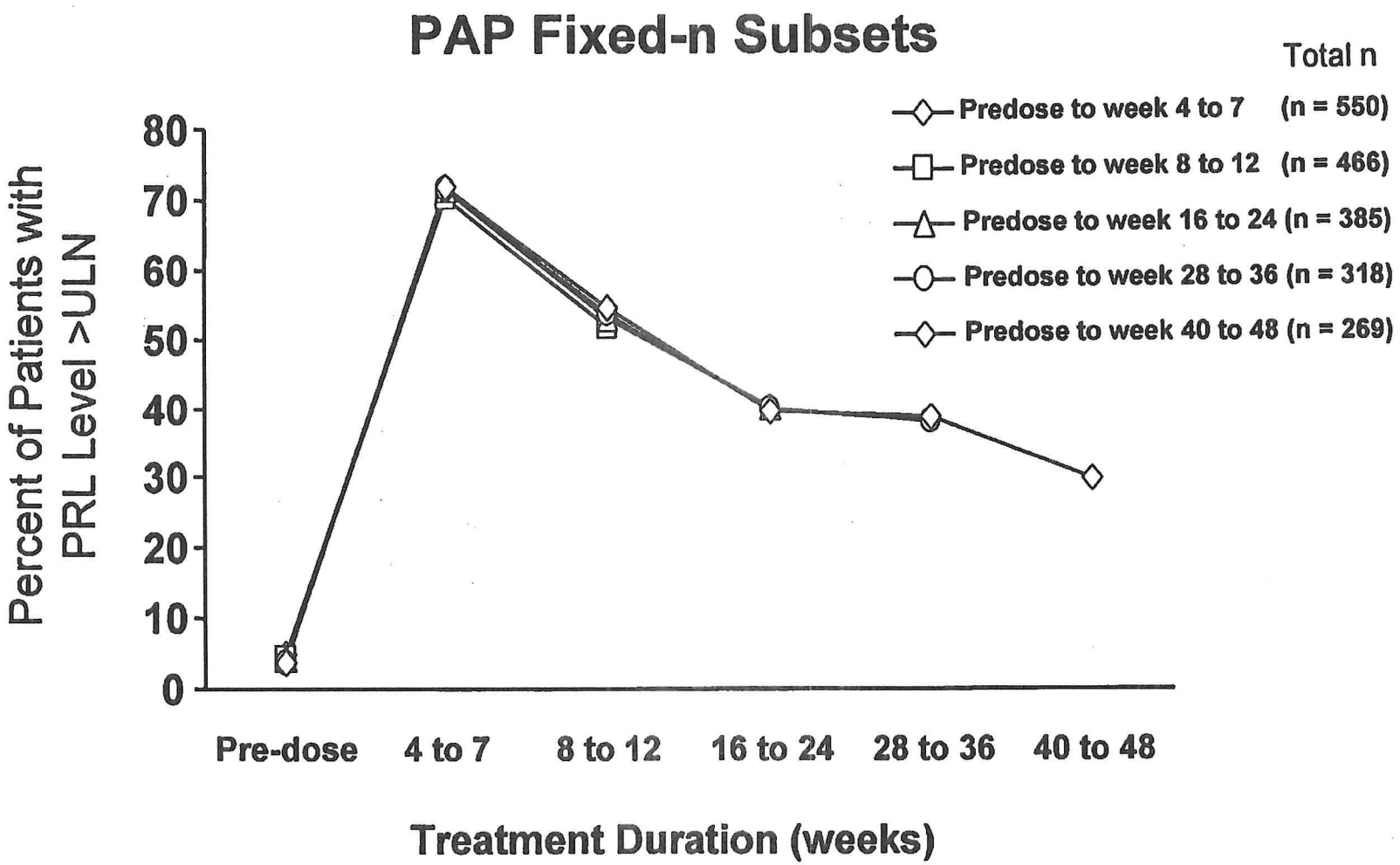
Prolactin Levels by Exposure



To be included in a subset, patients had to have PRL measurements at all time points

Data on file: Johnson & Johnson PRD, LLC

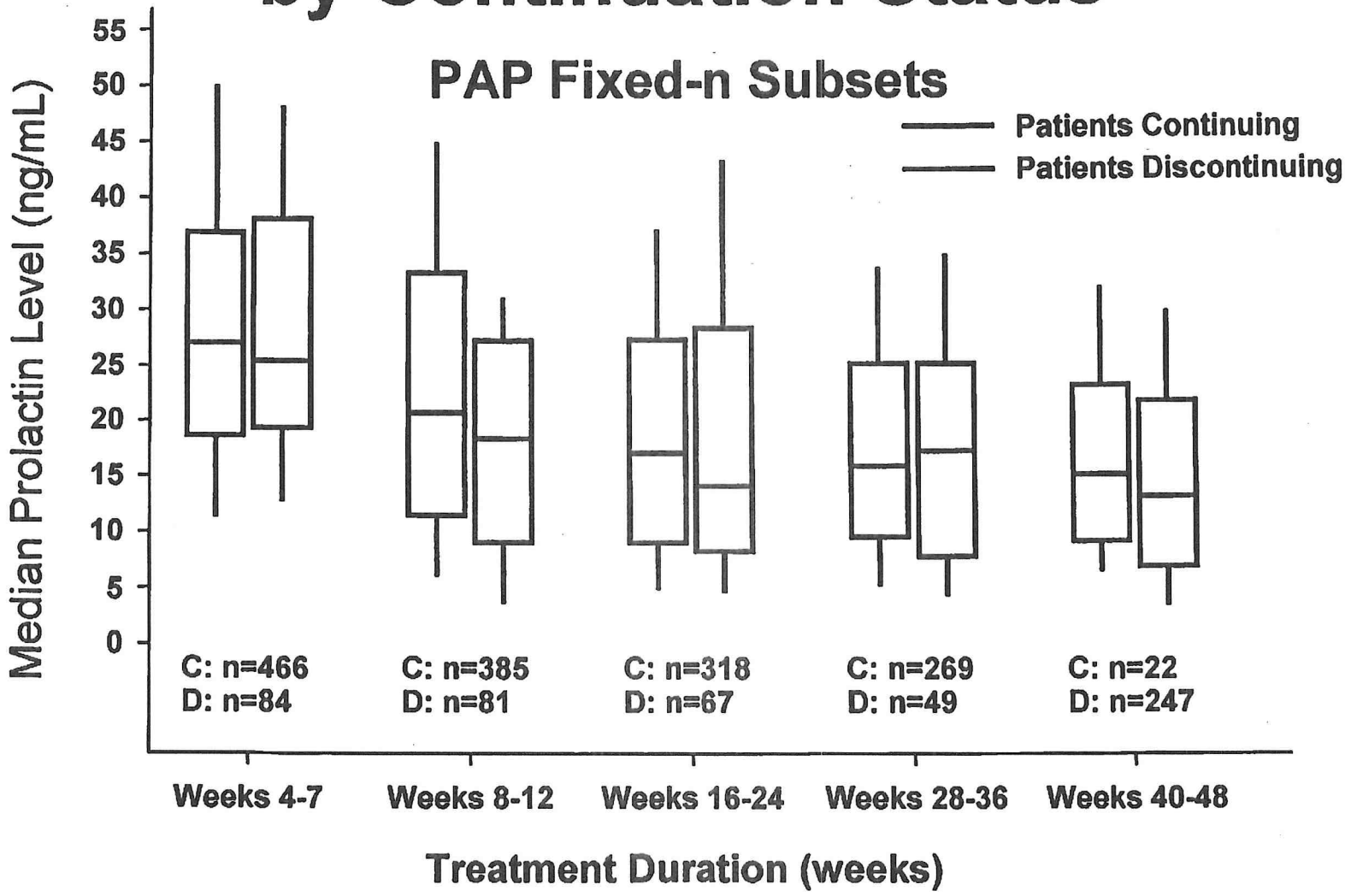
Prolactin Levels by Exposure



To be included in a subset, patients had to have PRL measurements at all time points

Data on file: Johnson & Johnson PRD, LLC

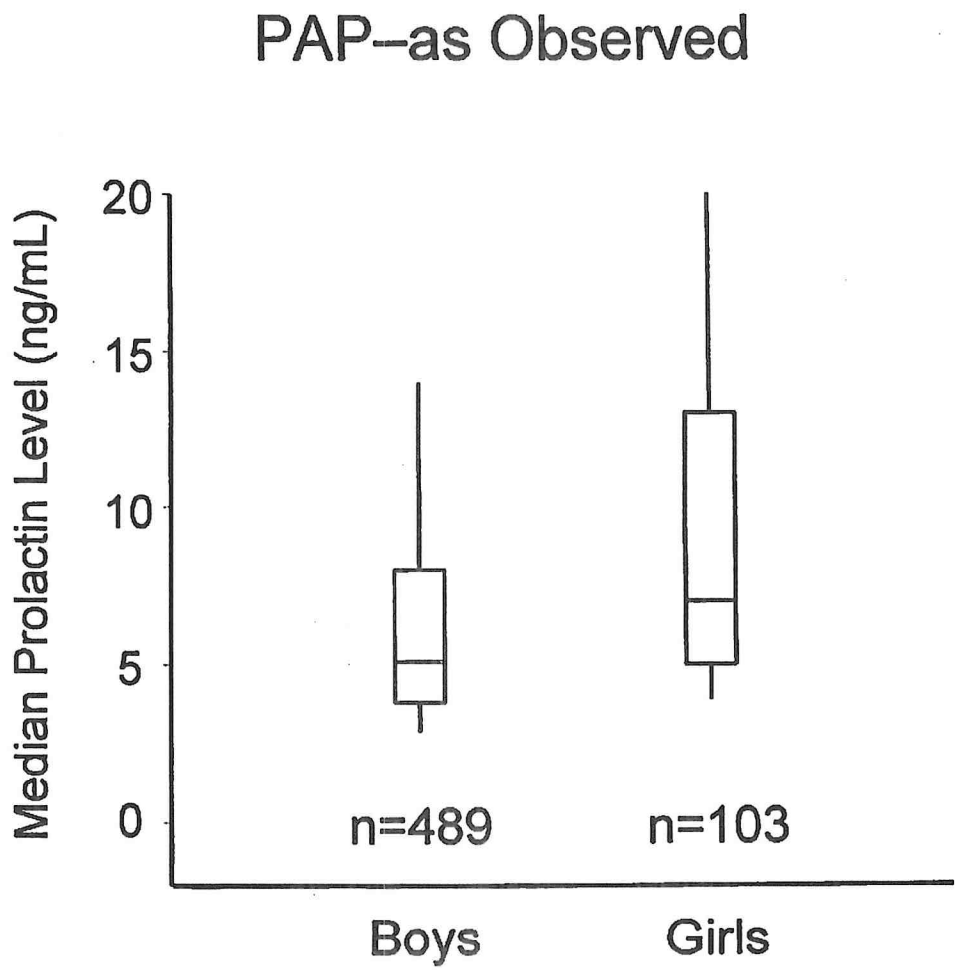
Prolactin Observations by Continuation Status



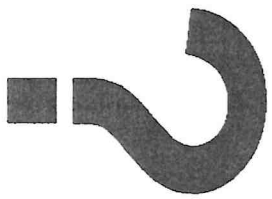
Data on file: Johnson & Johnson PRD, LLC

Gender and Age

Pre-dose Prolactin Level by Gender

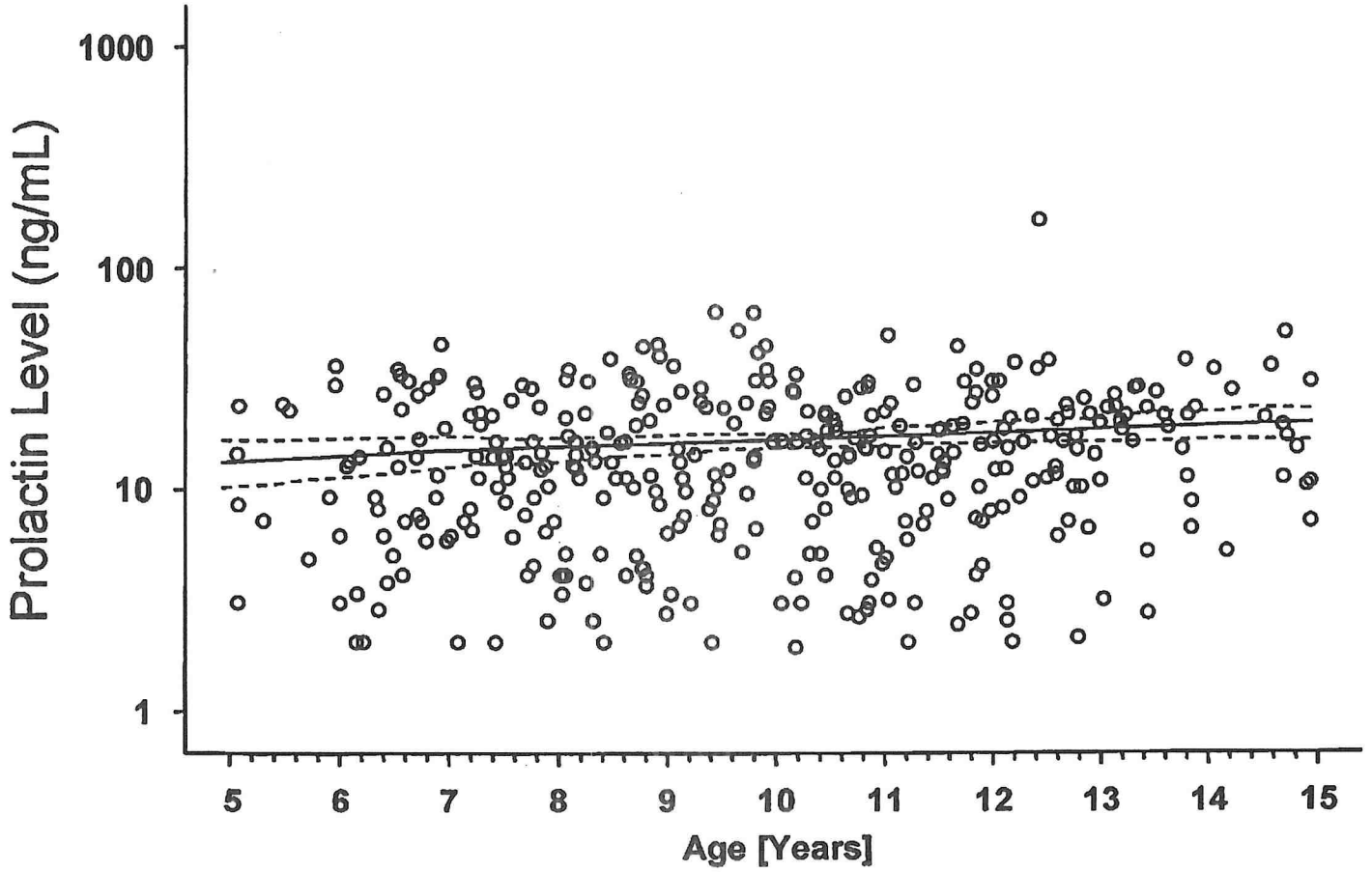


Data on file: Johnson & Johnson PRD, LLC



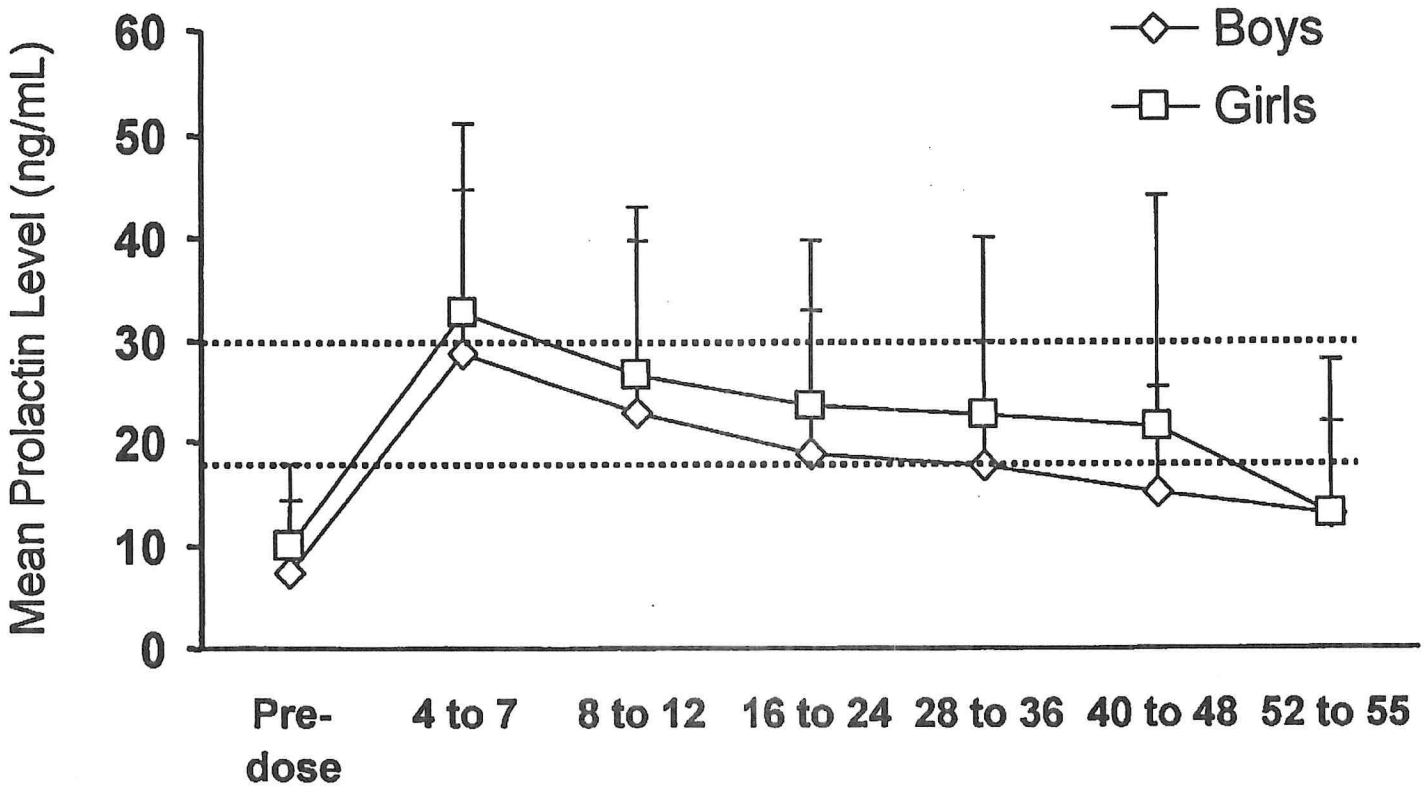
Prolactin Levels by Age

Weeks 40 to 48 (PAP–as Observed)



Data on file: Johnson & Johnson PRD, LLC

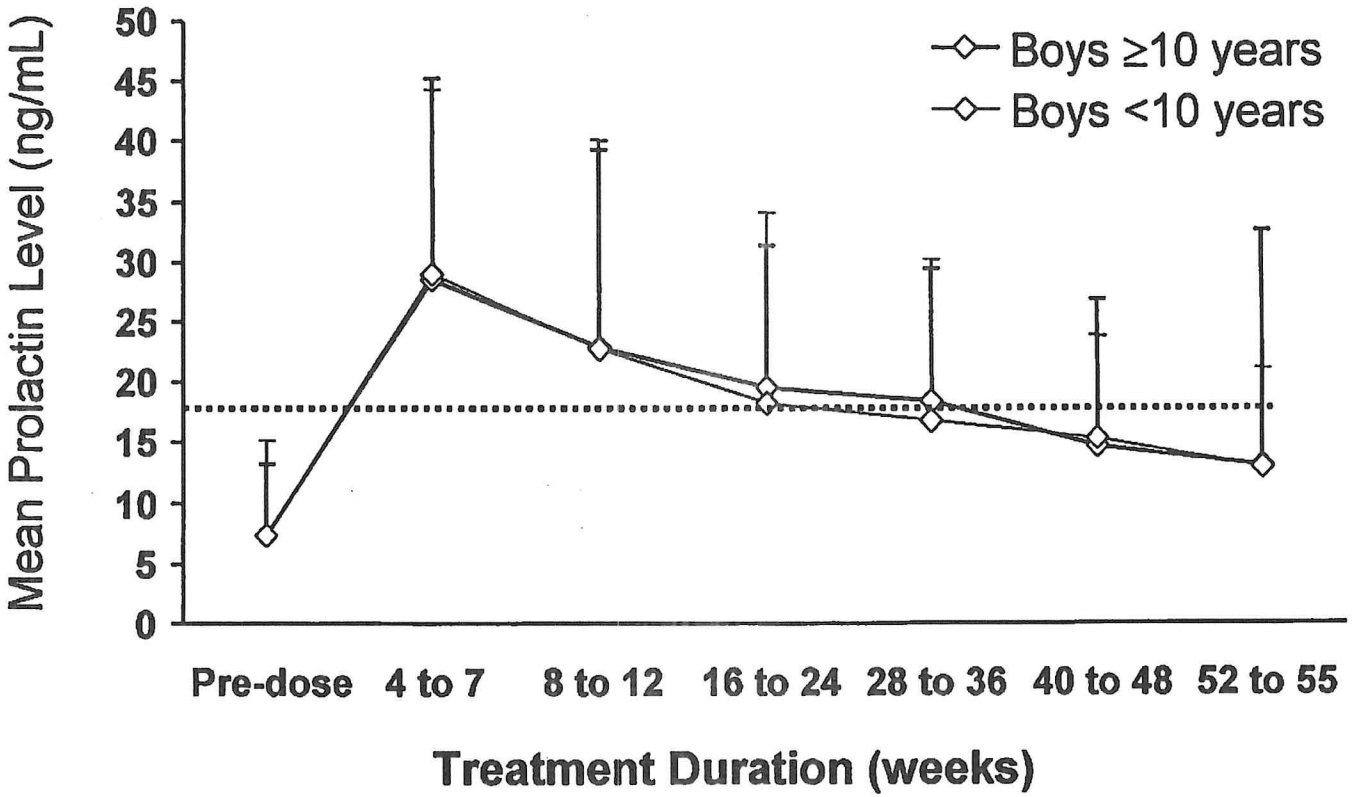
Prolactin Levels by Gender



Boys	n=489	n=457	n=417	n=369	n=323	n=303	n=34
Girls	n=103	n=93	n=82	n=72	n=71	n=55	n=8

Data on file: Johnson & Johnson PRD, LLC

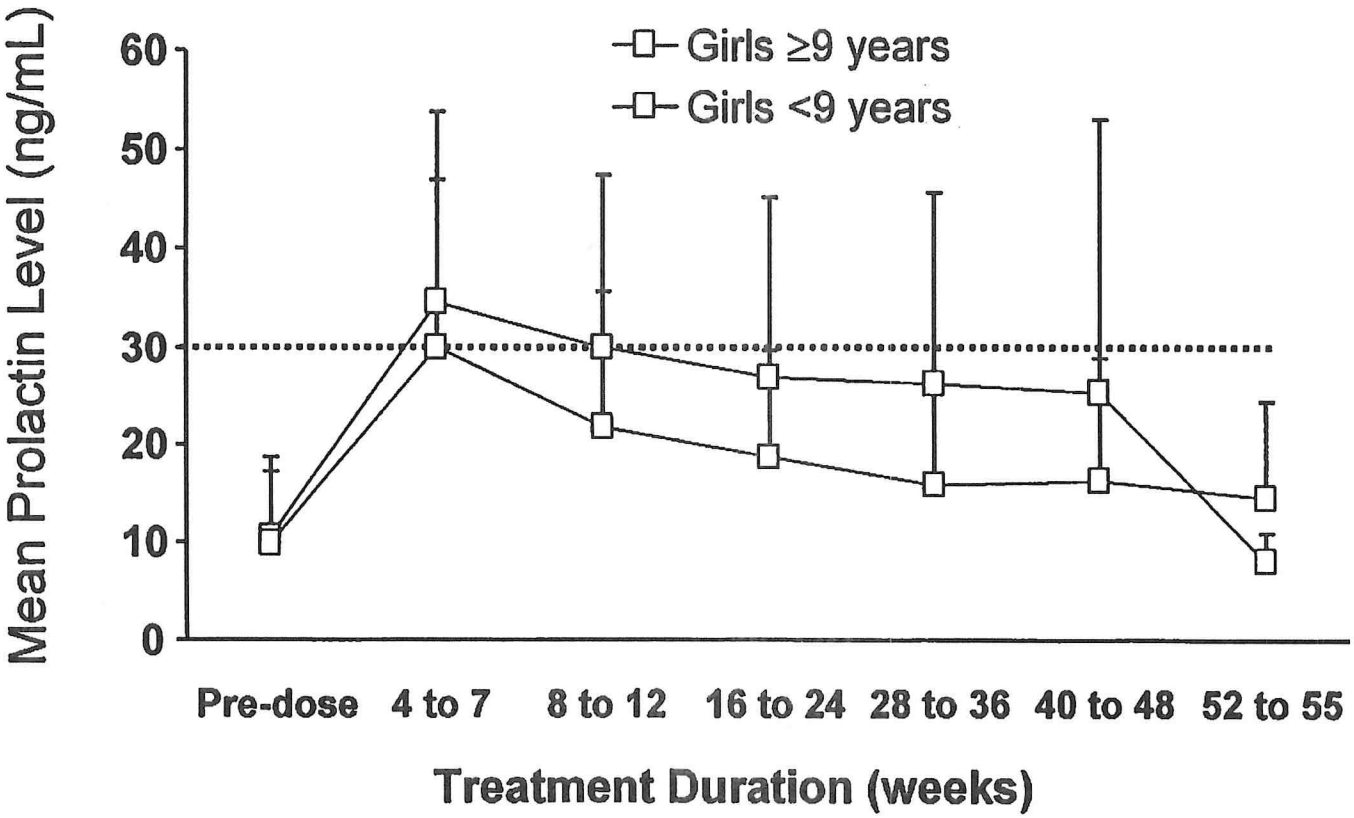
Prolactin Levels in Boys ≥10 vs <10 Years of Age



Boys ≥10	n=234	n=222	n=209	n=191	n=156	n=149	n=16
Boys <10	n=255	n=235	n=208	n=178	n=167	n=154	n=18

Data on file: Johnson & Johnson PRD, LLC

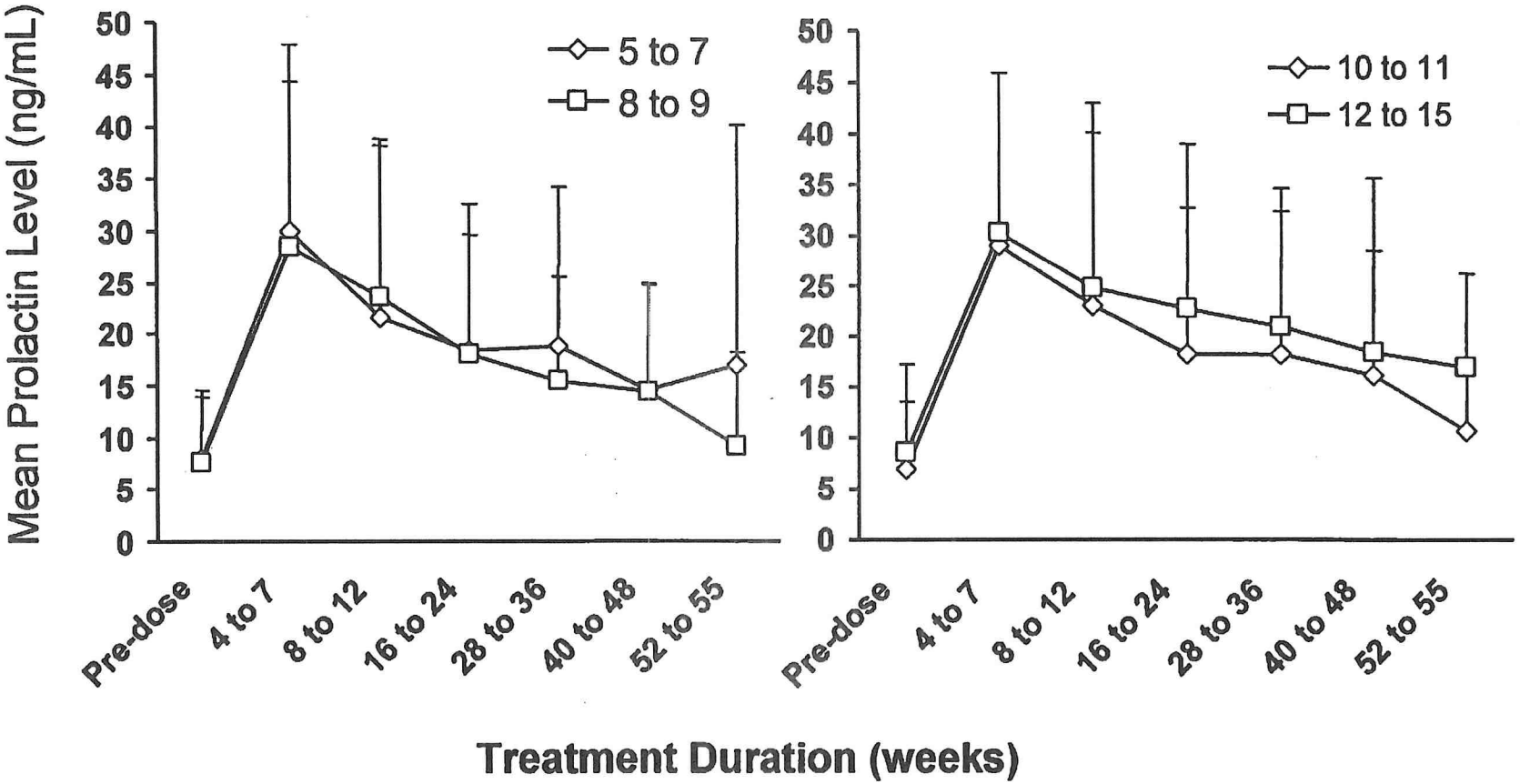
Prolactin Levels in Girls ≥9 vs <9 Years of Age



Girls ≥9	n=59	n=54	n=48	n=43	n=46	n=31	n=2
Girls <9	n=44	n=39	n=34	n=29	n=25	n=24	n=6

·Data on file: Johnson & Johnson PRD, LLC

Prolactin Levels by Age Group: All Patients



Data on file: Johnson & Johnson PRD, LLC

Correlation Between PRL Level and Age

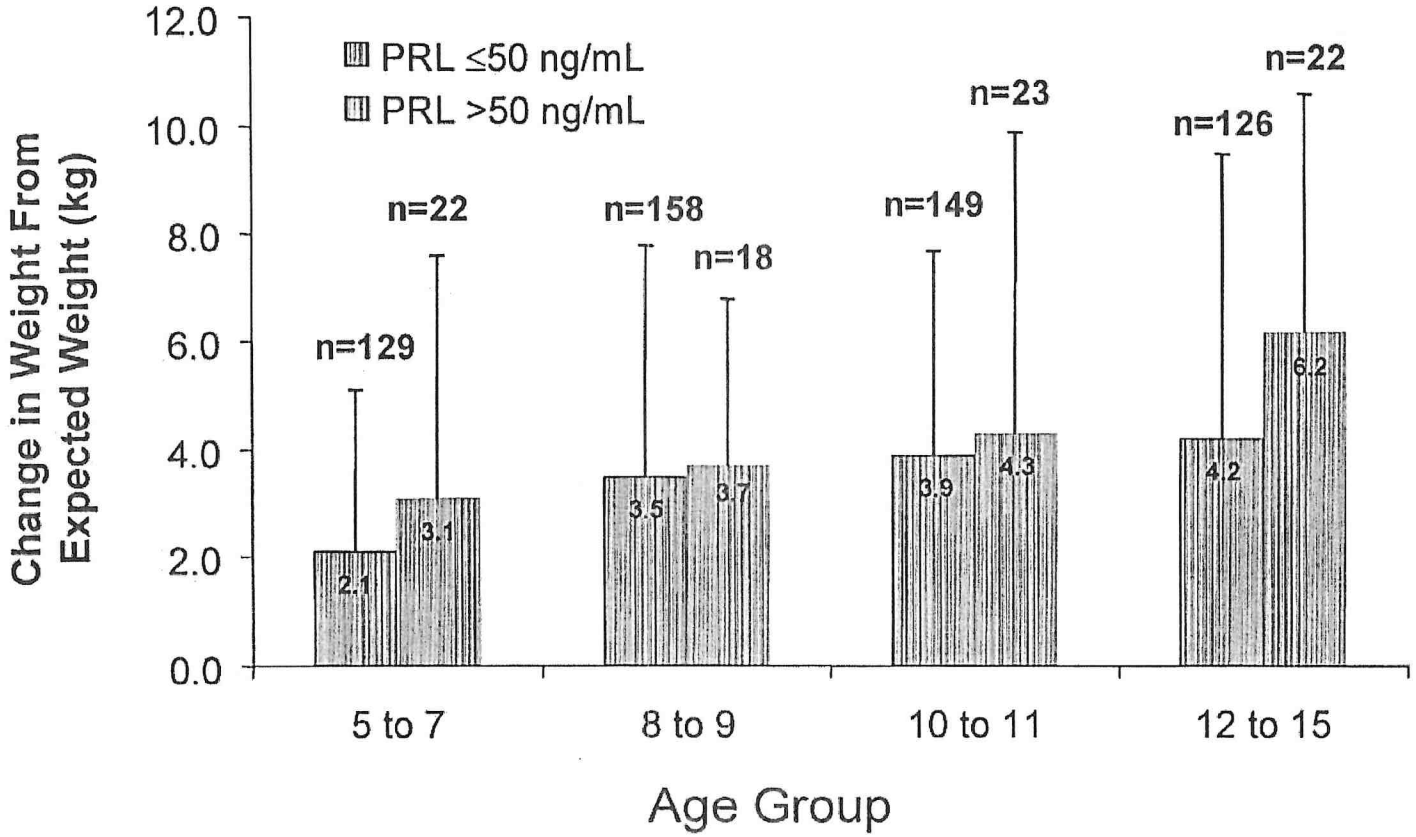
Exposure	n	Variance (Percent)*
Pre-dose	592	0.01
Weeks 4 to 7	550	0.19
Weeks 8 to 12	499	1.24
Weeks 16 to 24	441	1.48
Weeks 28 to 36	394	1.32
Weeks 40 to 48	358	1.76

***Percent of variation in PRL level that can be attributed to age; R^2 x 100**

Data on file: Johnson & Johnson PRD, LLC

Effects on Weight Gain

Change in Weight at Endpoint From Expected Weight: All Patients



Data on file: Johnson & Johnson PRD, LLC

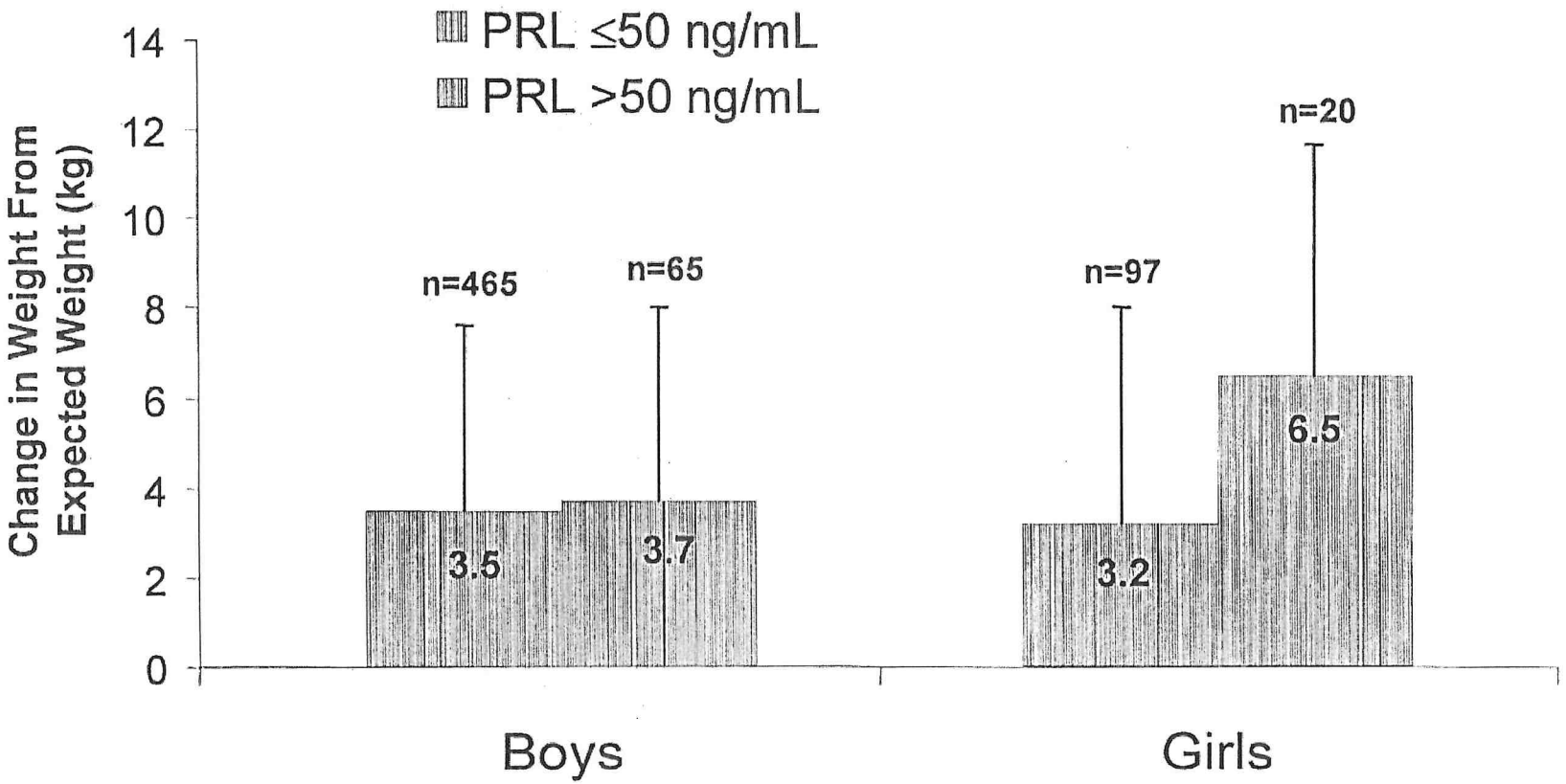
Analysis of Change in Weight at Endpoint From Expected Weight

- ≤50 vs >50
- Both genders
- All age groups

Factor	*P*-values
Age group	0.02
Gender	0.24
Age group x gender interaction	0.56
PRL	0.05
Age group x PRL interaction	0.92
Gender x PRL interaction	0.13
Age group x gender x PRL interaction	0.90

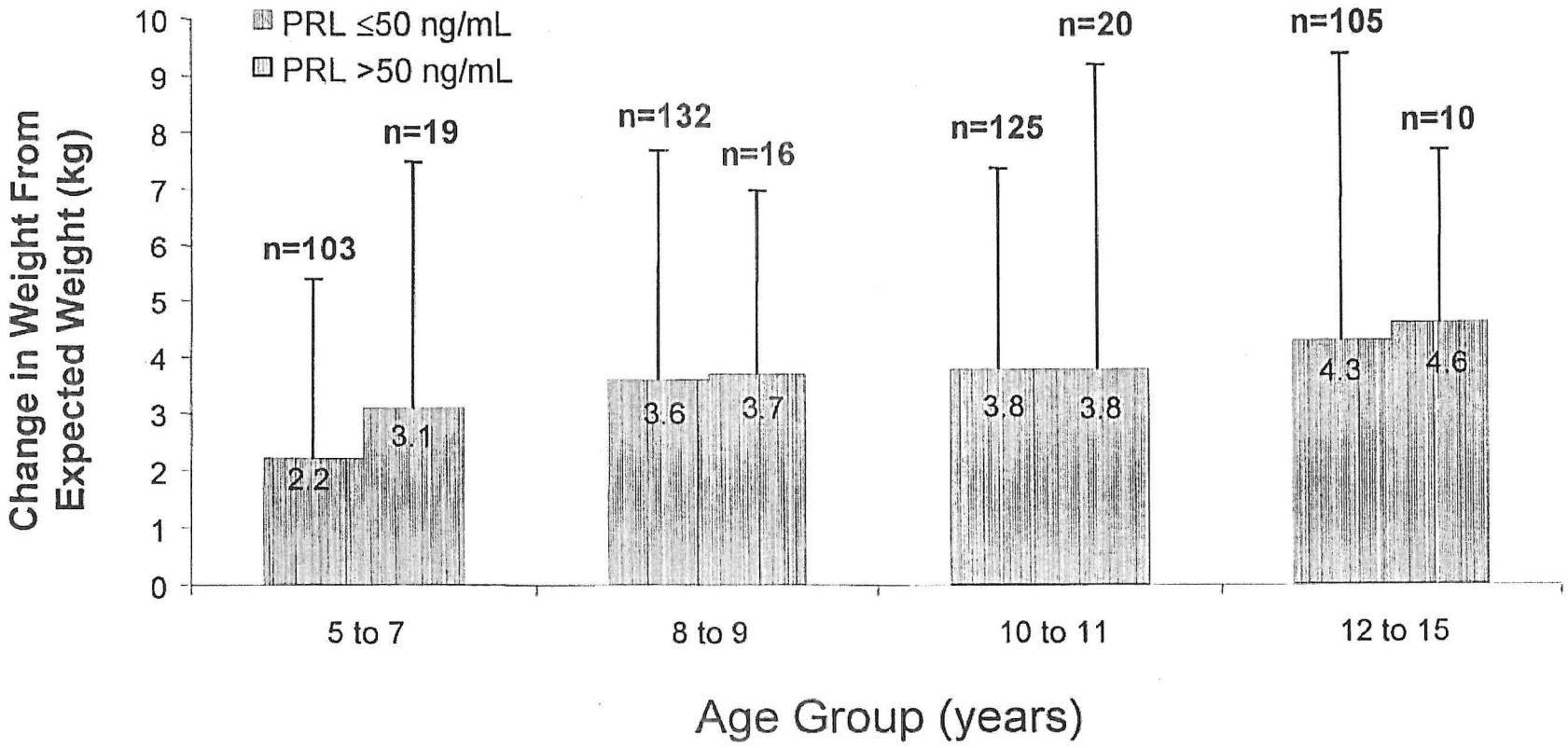
Data on file: Johnson & Johnson PRD, LLC

Change in Weight at Endpoint From Expected Weight



Data on file: Johnson & Johnson PRD, LLC

Change in Weight at Endpoint From Expected Weight in Boys



Data on file: Johnson & Johnson PRD, LLC

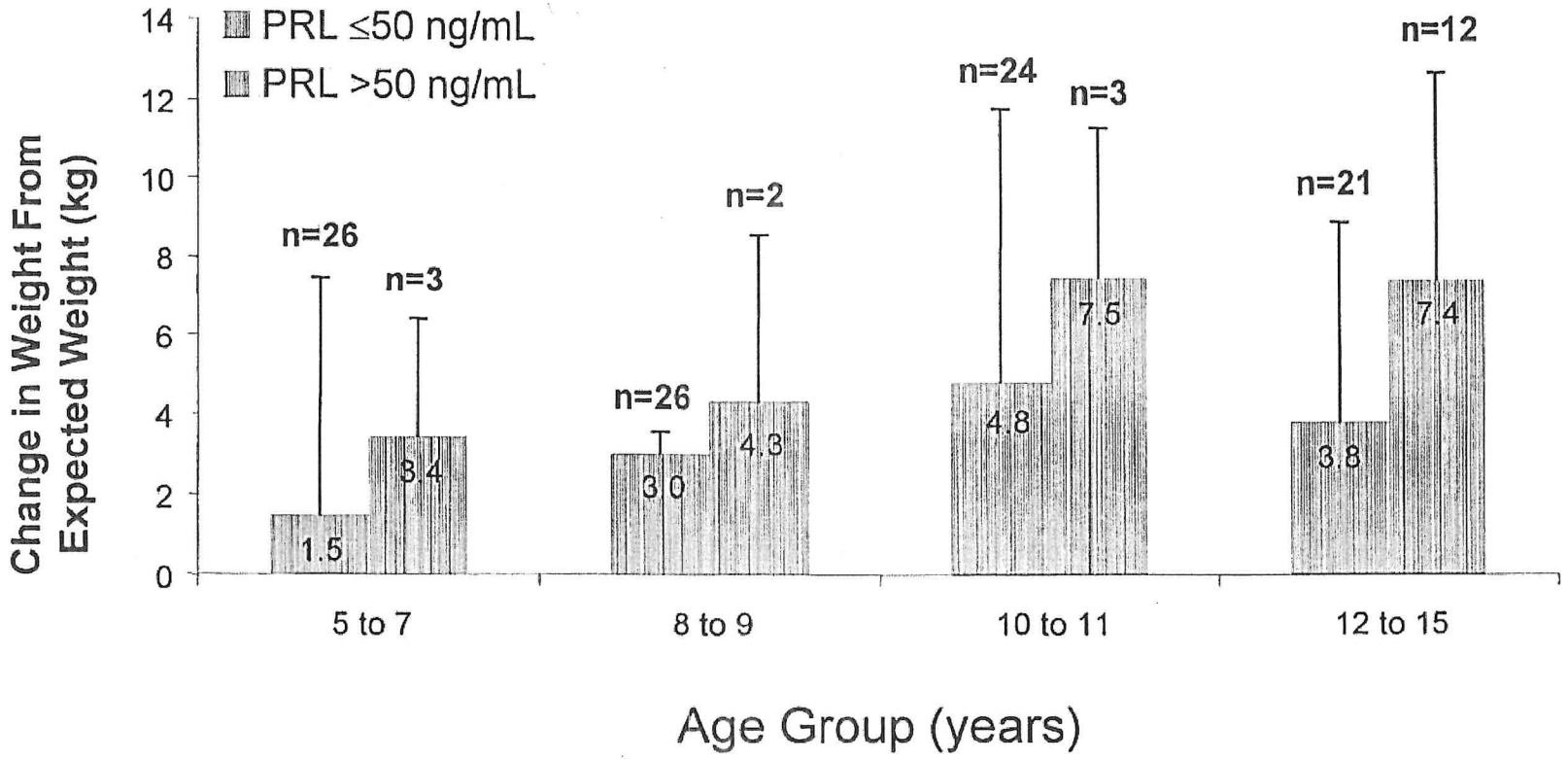
Analysis of Change in Weight at Endpoint From Expected Weight

- ≤50 vs >50
- Boys only
- All age groups

Factor	*P*-values
Age group	0.16
PRL	0.60
Age group x PRL interaction	0.93

·Data on file: Johnson & Johnson PRD, LLC

Change in Weight at Endpoint From Expected Weight in Girls



Data on file: Johnson & Johnson PRD, LLC

Analysis of Change in Weight at Endpoint From Expected Weight

- ≤50 vs >50
- Girls only
- All age groups

Factor	*P*-values
Age group	0.21
PRL	0.10
Age group x PRL interaction	0.92

Data on file: Johnson & Johnson PRD, LLC

Side Effects Hypothetically Attributable to Prolactin (SHAP)

Gahan Pandina, PhD
Assistant Director, Medical Affairs
Janssen Pharmaceutica Products, LP

SHAP by Baseline Tanner Stage

	Number (%) of Patients		
	ITT	PA	Non-PA
Total number of patients	700	592	108
Number of patients with at least one SHAP, n (%)	14 (2.0)	13 (2.2)	1 (0.9)
Tanner stage, n			
1		4	
2		2	
3		4	
4		3	
5		0	

In the PA population, mean onset of the first SHAP was 98.8 days (minimum 1 day and maximum 254 days)

Data on file: Johnson & Johnson PRD, LLC

Definitions

- Preferred terms excluded from analysis per pediatric endocrinologists:
  - Dysmenorrhea
  - Growth hormone excess
  - Hyperprolactinemia
  - Penis disorder
  - Sexual function abnormal
  - Testis disorder
  - Vaginitis atrophic
- Patients with ≥1 week of amenorrhea, girls with ≥31 days of gynecomastia and boys <10 years of age with gynecomastia are included

Data on file: Johnson & Johnson PRD, LLC

Individual SHAP

	Number (%) of Patients		
	ITT	PA	Non-PA
Endocrine disorders	5 (0.7)	5 (0.8)	0 (0.0)
Gynecomastia	5 (0.7)	5 (0.8)	0 (0.0)
Reproductive disorders, female	9 (1.3)	8 (1.4)	1 (0.9)
Amenorrhea	4 (0.6)	3 (0.5)	1 (0.9)
Menorrhagia	3 (0.4)	3 (0.5)	0 (0.0)
Breast enlargement	1 (0.1)	1 (0.2)	0 (0.0)
Lactation nonpuerperal	1 (0.1)	1 (0.2)	0 (0.0)
Menstrual disorder	1 (0.1)	1 (0.2)	0 (0.0)
Vaginal hemorrhage	1 (0.1)	1 (0.2)	0 (0.0)

Data on file: Johnson & Johnson PRD, LLC

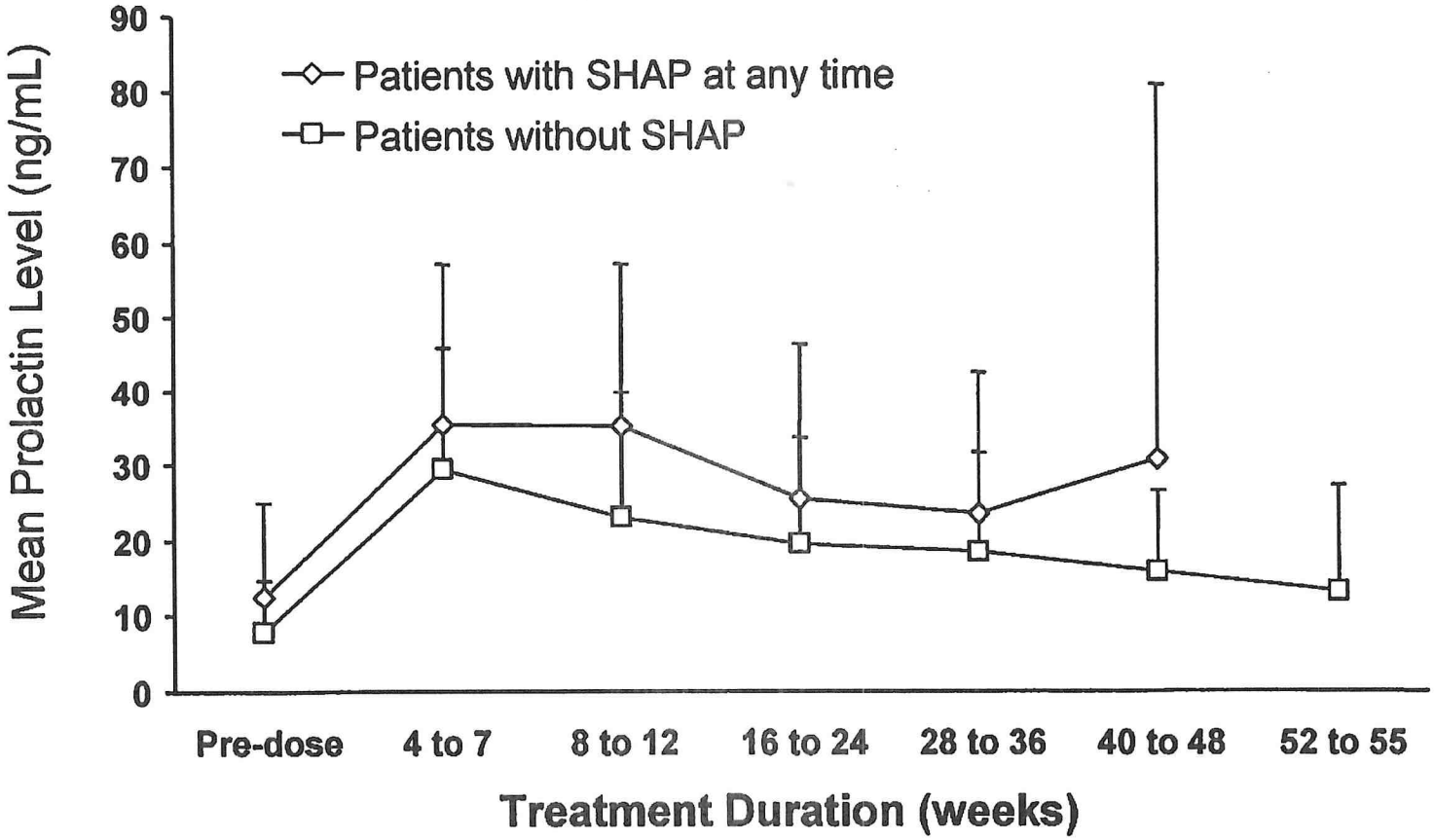
Risperidone Dosing Information in Patients With and Without SHAP

PAP - as Observed

	Patients with SHAP at any time (n=13)	Patients without SHAP (n=579)
Duration (days) Mean (±SD) Median (range)	 358 (31.2) 365 (288 to 414)	 318 (102.1) 360 (28 to 505)
Average daily dose (mg/day) Mean (±SD) Median (range)	 1.29 (0.60) 1.20 (0.12 to 2.29)	 1.26 (0.71) 1.23 (0.001 to 4.17)
Mean (±SD) age of patients with SHAP Boys Girls	 7.8 (1.7) 12.8 (1.8)	 NA NA

Data on file: Johnson & Johnson PRD, LLC

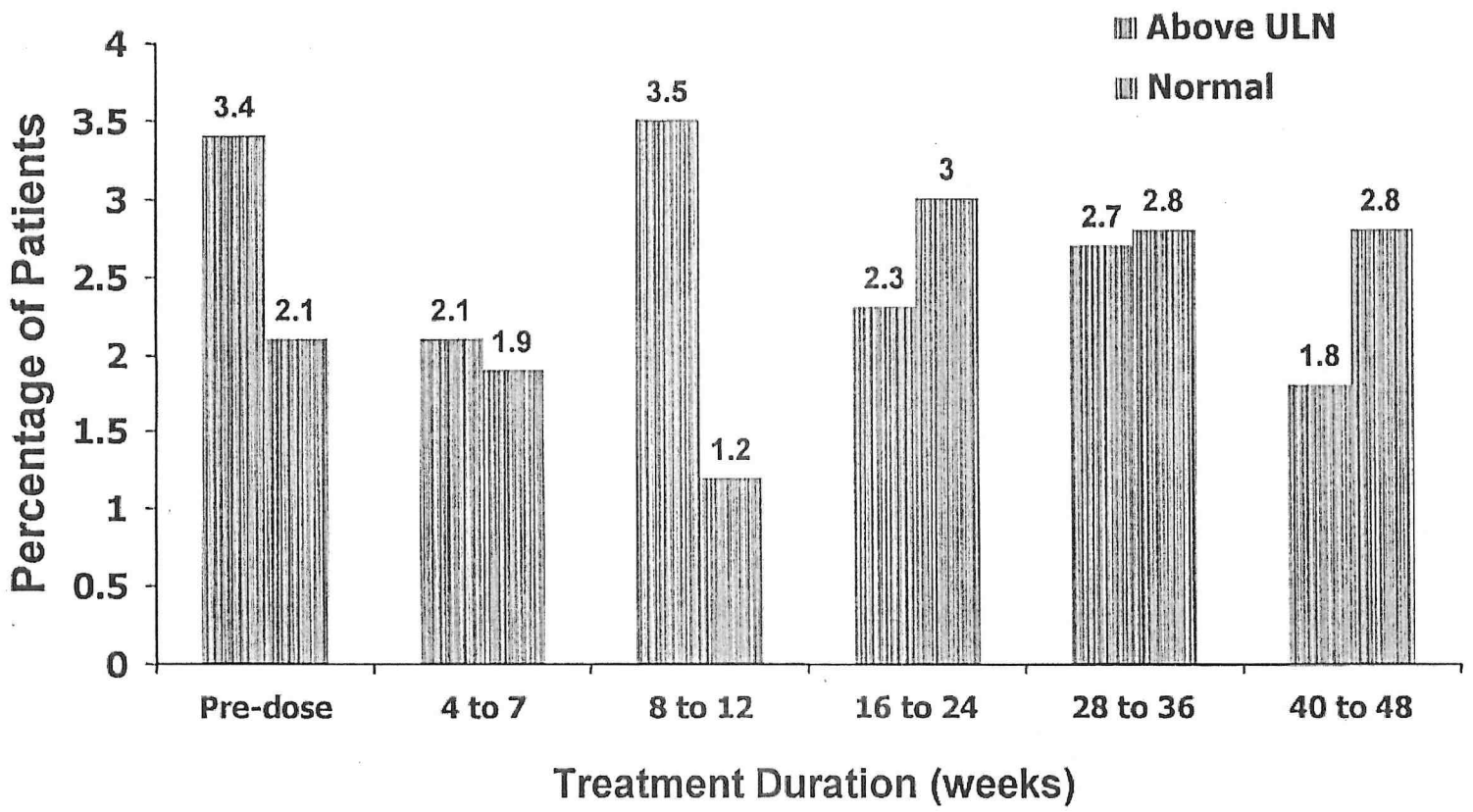
Prolactin Levels in Patients With and Without SHAP



+SHAP	n=13	n=11	n=12	n=12	n=11	n=9	n=0
–SHAP	n=579	n=539	n=487	n=429	n=383	n=349	n=42

Data on file: Johnson & Johnson PRD, LLC

Percent of Patients with SHAP: Normal Versus Above ULN



n	12/563 1/29	3/162 8/388	3/242 9/257	8/265 4/176	7/246 4/148	7/248 2/110	Normal >ULN
P-values	.64	.87	.09	.64	.93	.58	

Data on file: Johnson & Johnson PRD, LLC

Motor Effects

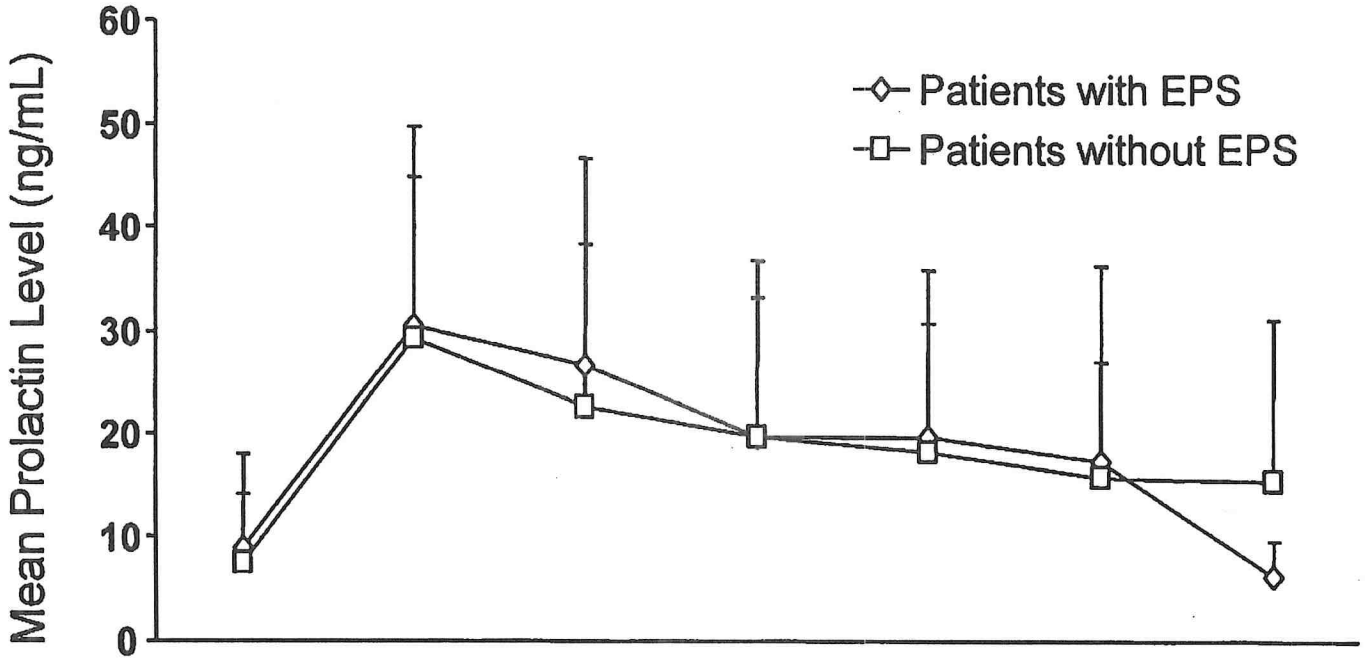
Incidence of Motor Effects

	Number (%) of Patients		
	ITT (n = 700)	PA (n = 592)	Non-PA (n = 108)
Number of patients with at least one EPS	147 (21.0)	129 (21.8)	18 (16.7)
CNS and PNS disorders	147 (21.0)	129 (21.8)	18 (16.7)
Hypertonia	37 (5.3)	34 (5.7)	3 (2.8)
Tremor	33 (4.7)	27 (4.6)	6 (5.6)
Extrapyramidal disorder	29 (4.1)	28 (4.7)	1 (0.9)
Hyperkinesia	24 (3.4)	22 (3.7)	2 (1.9)
Hypokinesia	22 (3.1)	19 (3.2)	3 (2.8)
Involuntary muscle contractions	21 (3.0)	20 (3.4)	1 (0.9)
Bradykinesia	14 (2.0)	12 (2.0)	2 (1.9)
Dystonia	11 (1.6)	9 (1.5)	2 (1.9)
Oculogyric crisis	6 (0.9)	4 (0.7)	2 (1.9)
Tardive dyskinesia	2 (0.3)	2 (0.3)	0
Hypotonia	1 (0.1)	1 (0.2)	0

In the PA population, mean onset of first EPS was 64.3 days (minimum 1 day and maximum 369 days)

·Data on file: Johnson & Johnson PRD, LLC

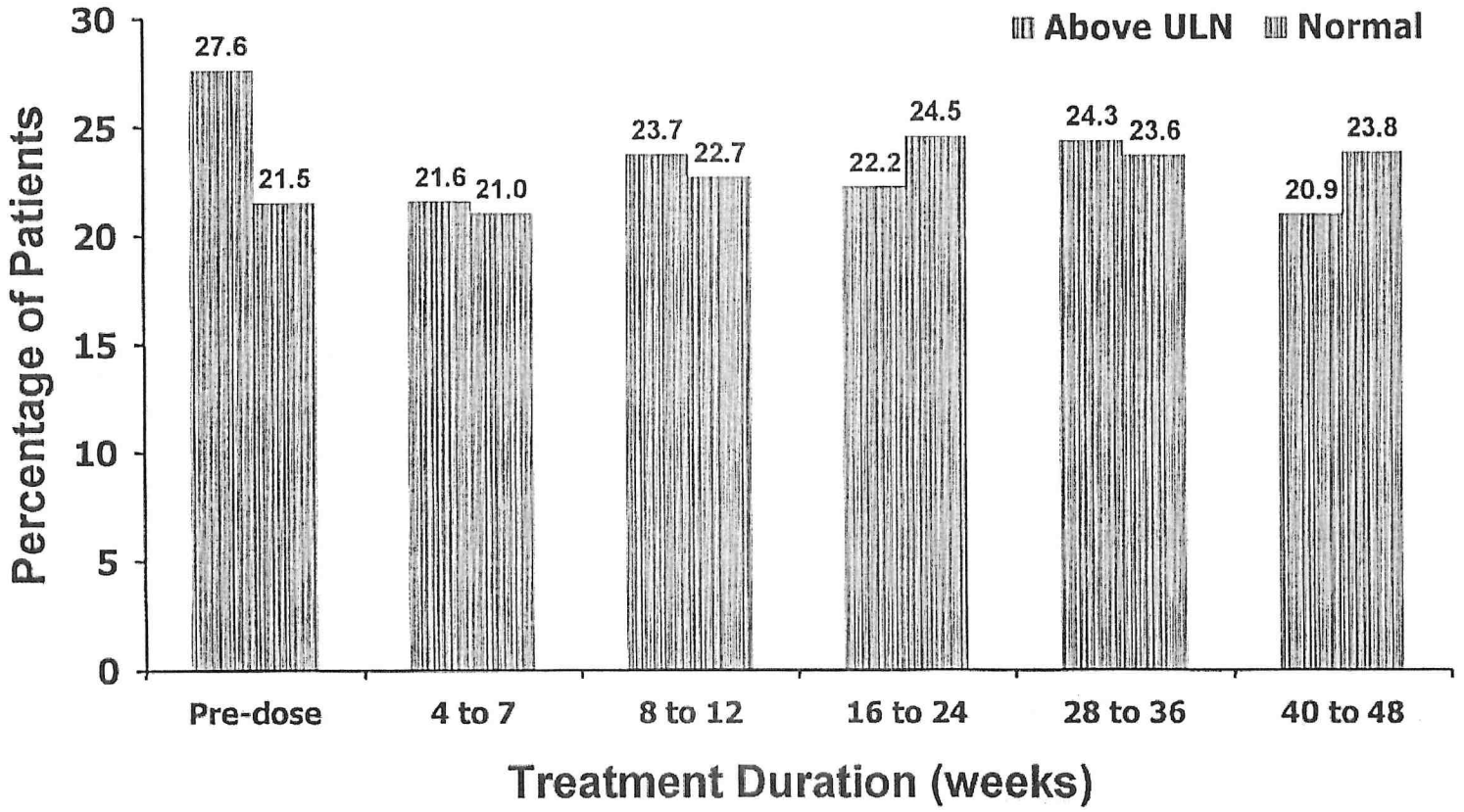
Prolactin Levels in Patients With and Without EPS



+EPS	n=129	n=118	n=116	n=104	n=94	n=82	n=11
–EPS	n=463	n=432	n=383	n=337	n=300	n=276	n=31

Data on file: Johnson & Johnson PRD, LLC

Percent of Patients with EPS by PRL Level: Normal vs Above ULN

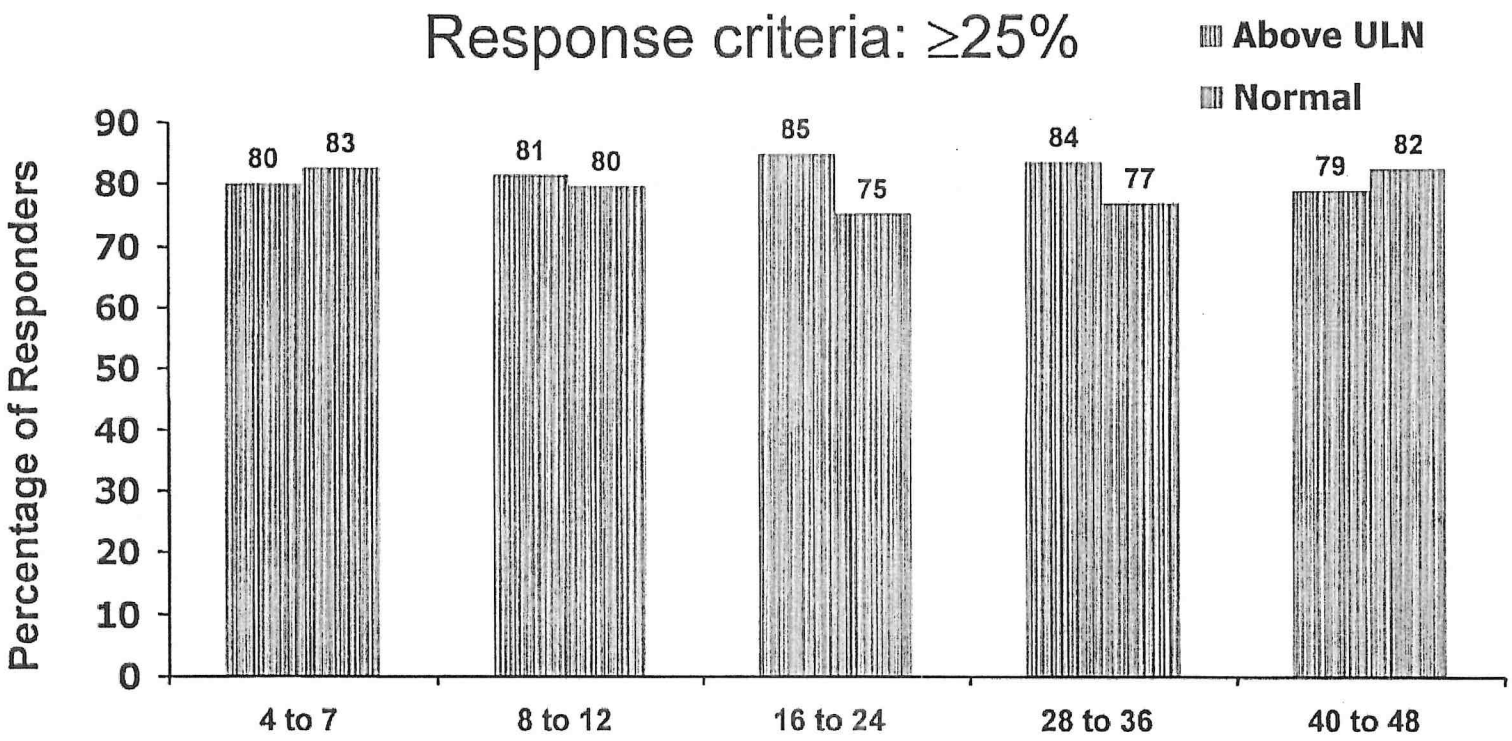


n	121/563 8/29	34/162 84/388	55/242 61/257	65/265 39/176	58/246 36/148	59/248 23/110	Normal >ULN
P-values	.44	.86	.79	.57	.87	.55	

Data on file: Johnson & Johnson PRD, LLC

NCBRF Responders

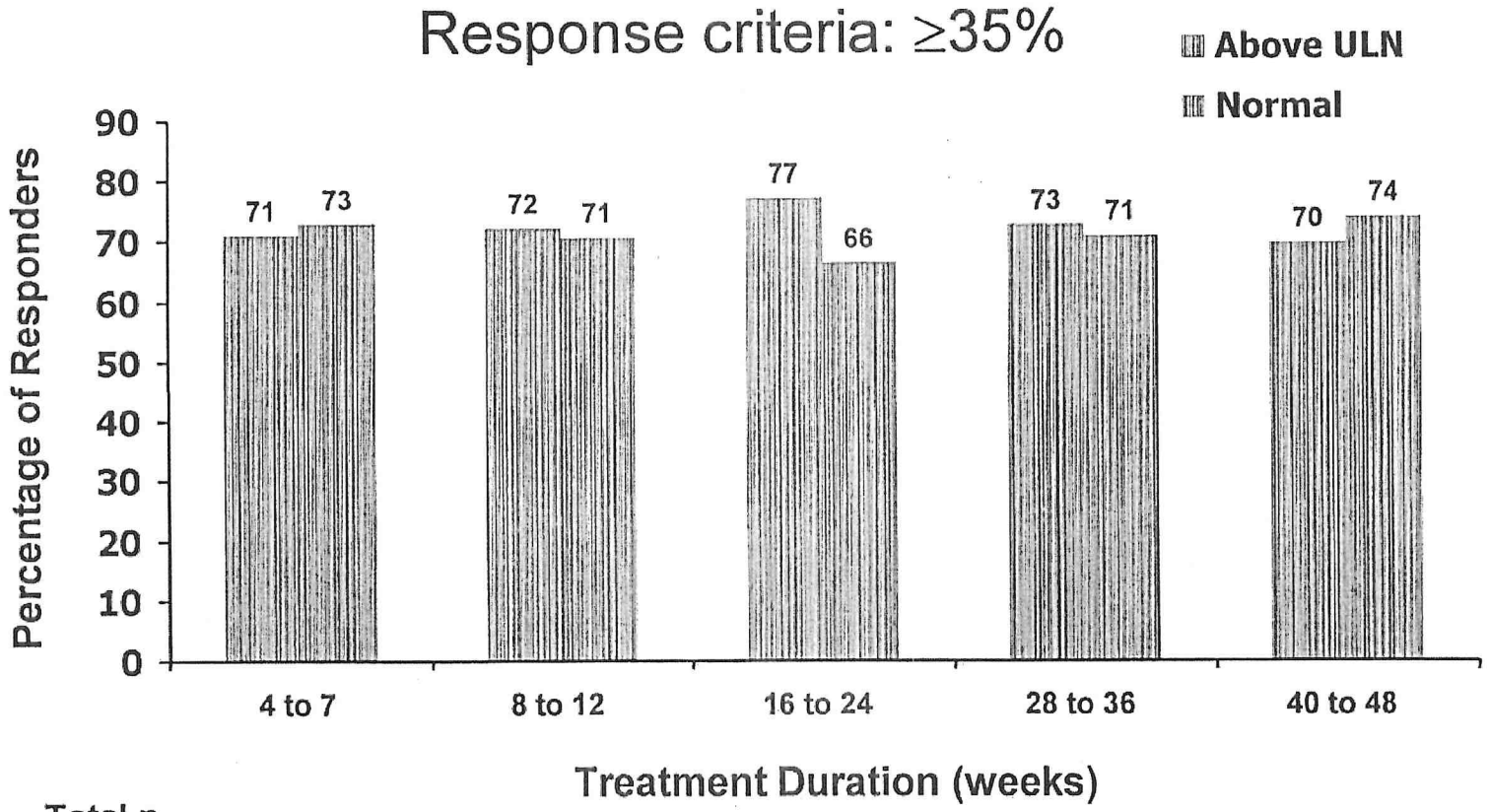
Responders on the Conduct Problem Subscale of the NCBRF Versus PRL Level



Total n					
Normal	92	147	193	195	245
>ULN	243	183	126	121	109
P-values	**.62**	**.68**	**.04**	**.16**	**.43**

Data on file: Johnson & Johnson PRD, LLC

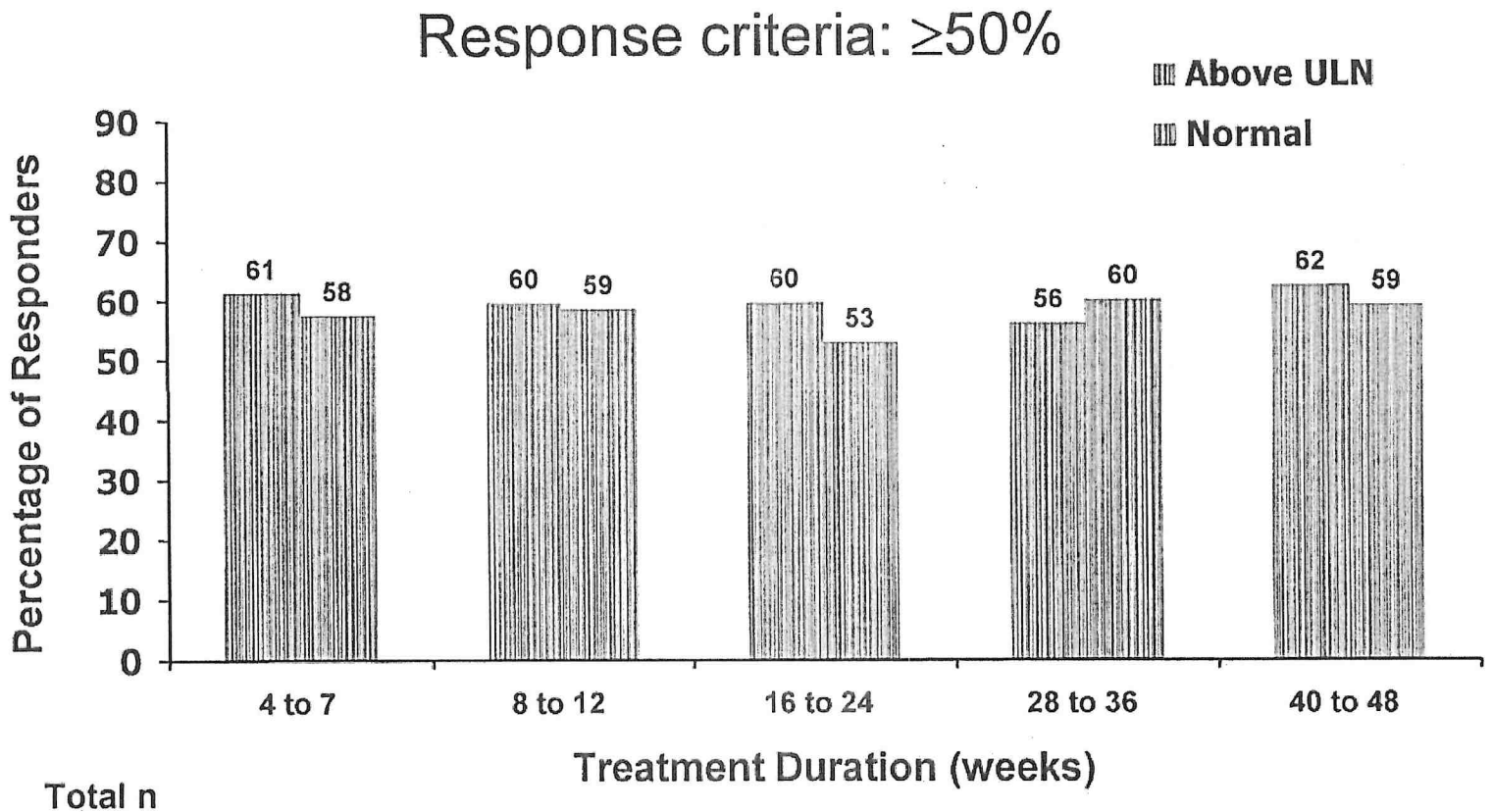
Responders on the Conduct Problem Subscale of the NCBRF Versus PRL Level



Total n					
Normal	92	147	193	195	245
>ULN	243	183	126	121	109
P-values	**.77**	**.78**	**.04**	**.71**	**.42**

*Data on file: Johnson & Johnson PRD, LLC

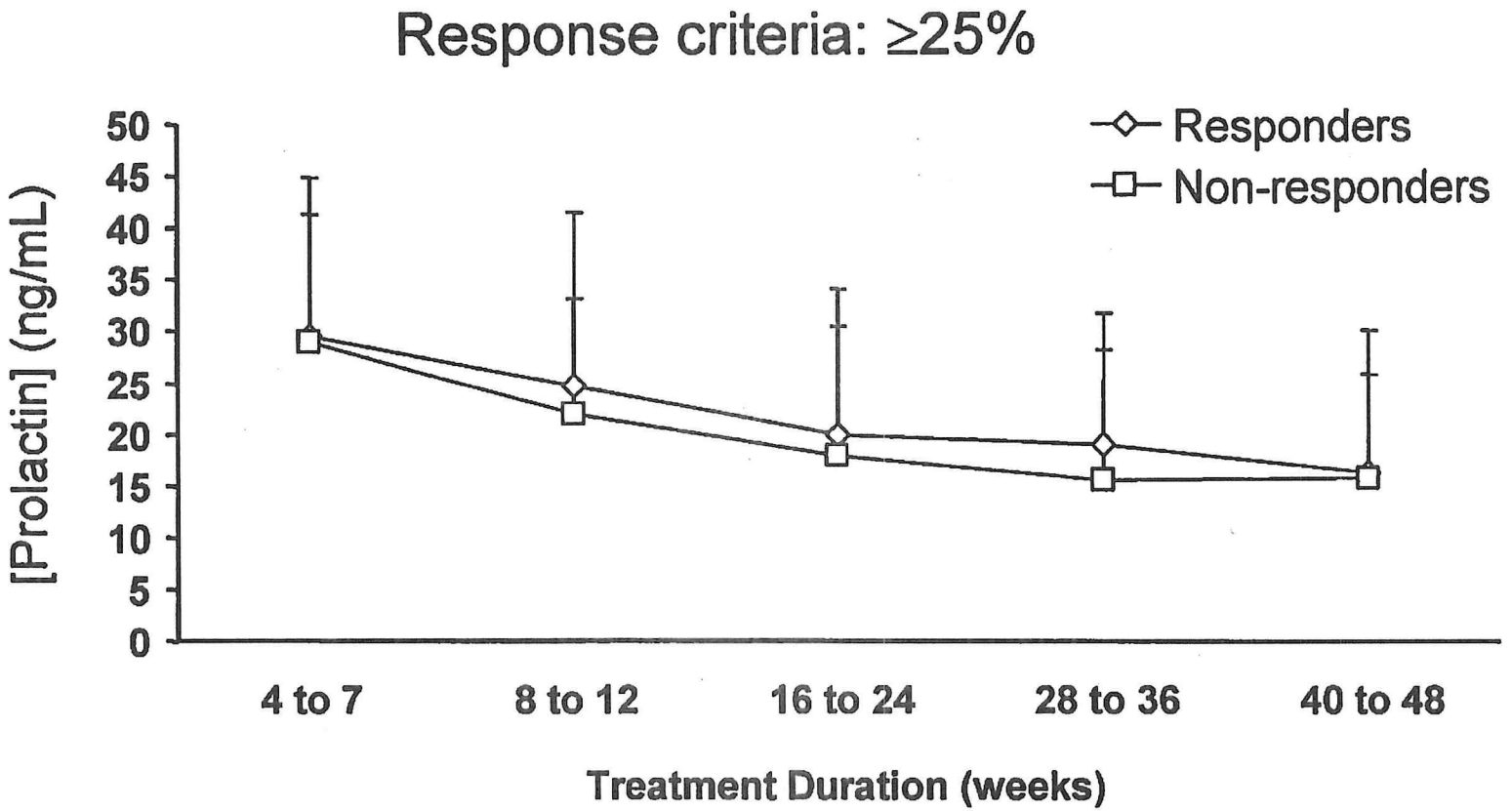
Responders on the Conduct Problem Subscale of the NCBRF Versus PRL Level



Total n					
Normal	92	147	193	195	245
>ULN	243	183	126	121	109
P-values	**.54**	**.85**	**.24**	**.50**	**.57**

Data on file: Johnson & Johnson PRD, LLC

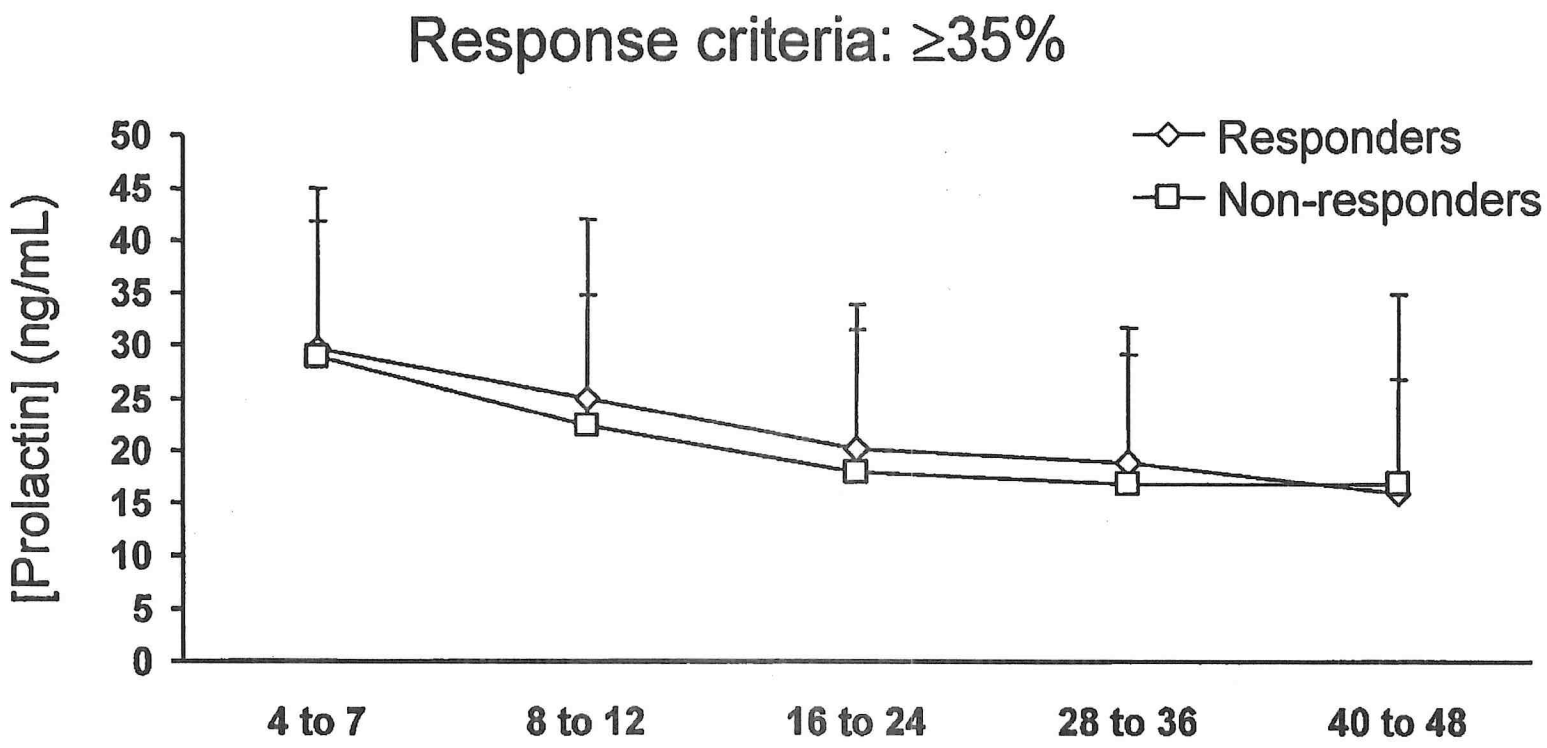
PRL Levels In Responders on the Conduct Problem Subscale of the NCBRF Versus Non-responders



n					
Responders	271	266	252	251	288
Non-responders	64	64	67	65	66

Data on file: Johnson & Johnson PRD, LLC

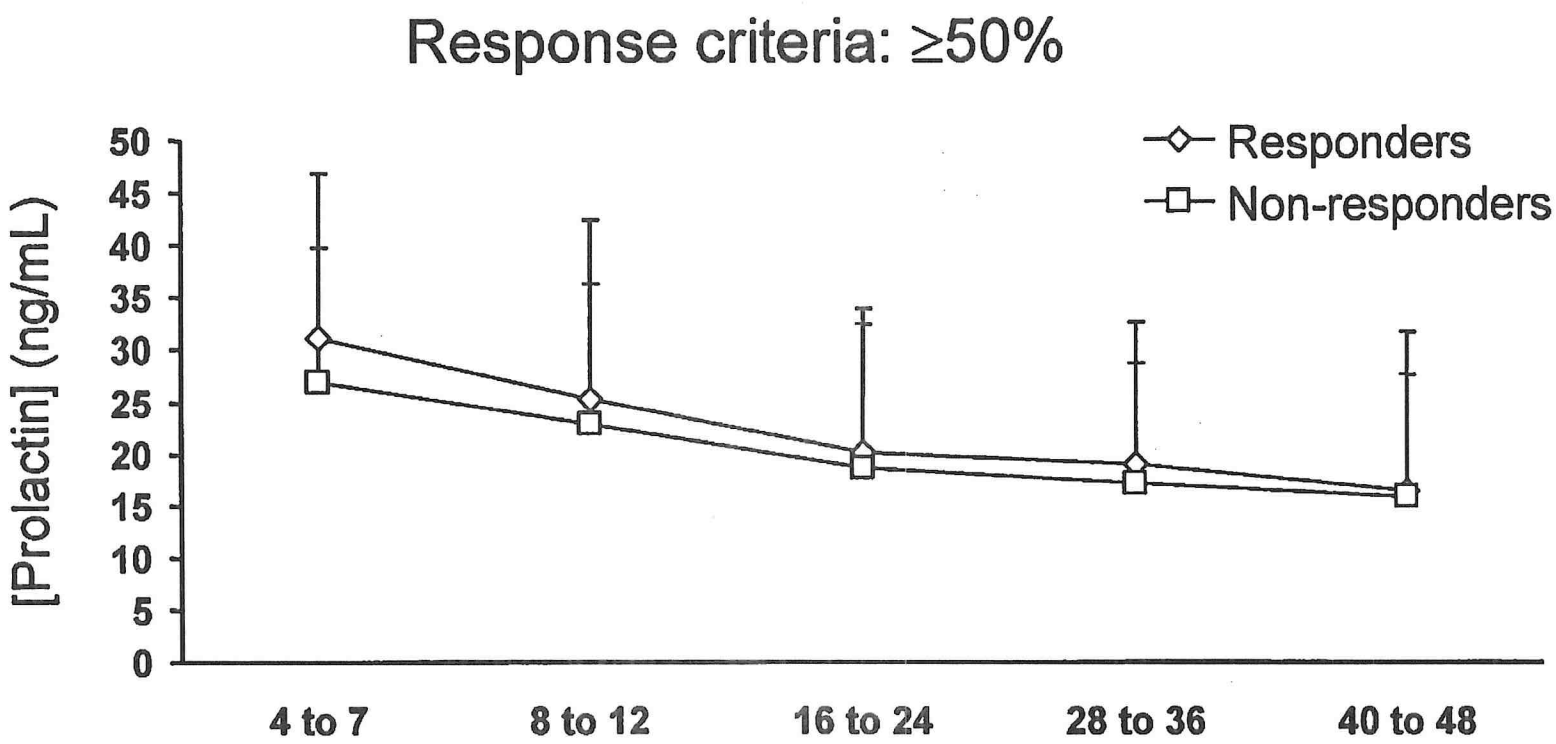
PRL Levels In Responders on the Conduct Problem Subscale of the NCBRF Versus Non-responders



n					
Responders	240	236	225	226	257
Non-responders	95	94	94	90	97

*Data on file: Johnson & Johnson PRD, LLC

PRL Levels In Responders on the Conduct Problem Subscale of the NCBRF Versus Non-responders

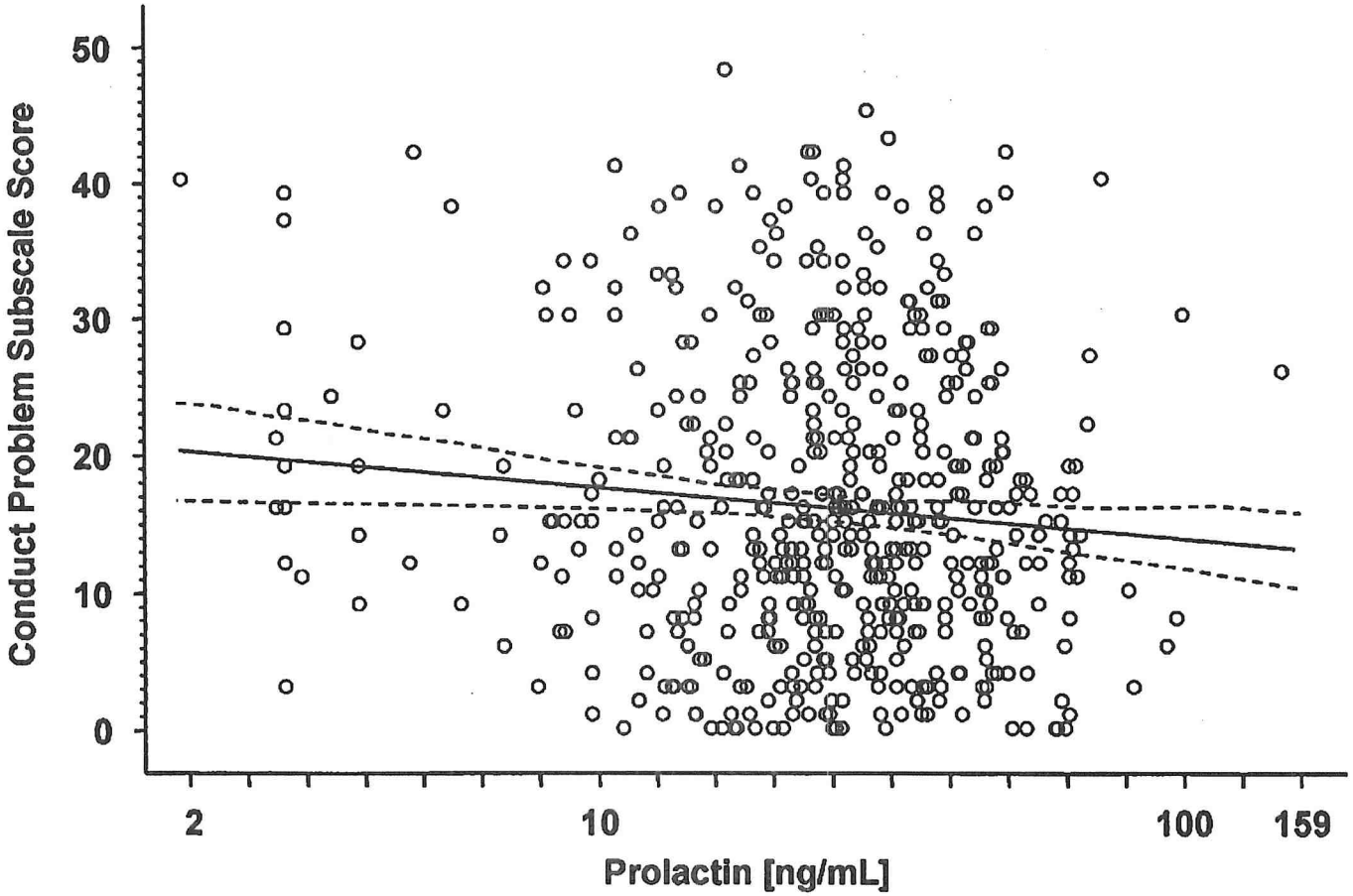


n					
Responders	202	195	177	185	213
Non-responders	133	135	142	131	141

Data on file: Johnson & Johnson PRD, LLC

Conduct Problem Subscale Score vs Prolactin Levels

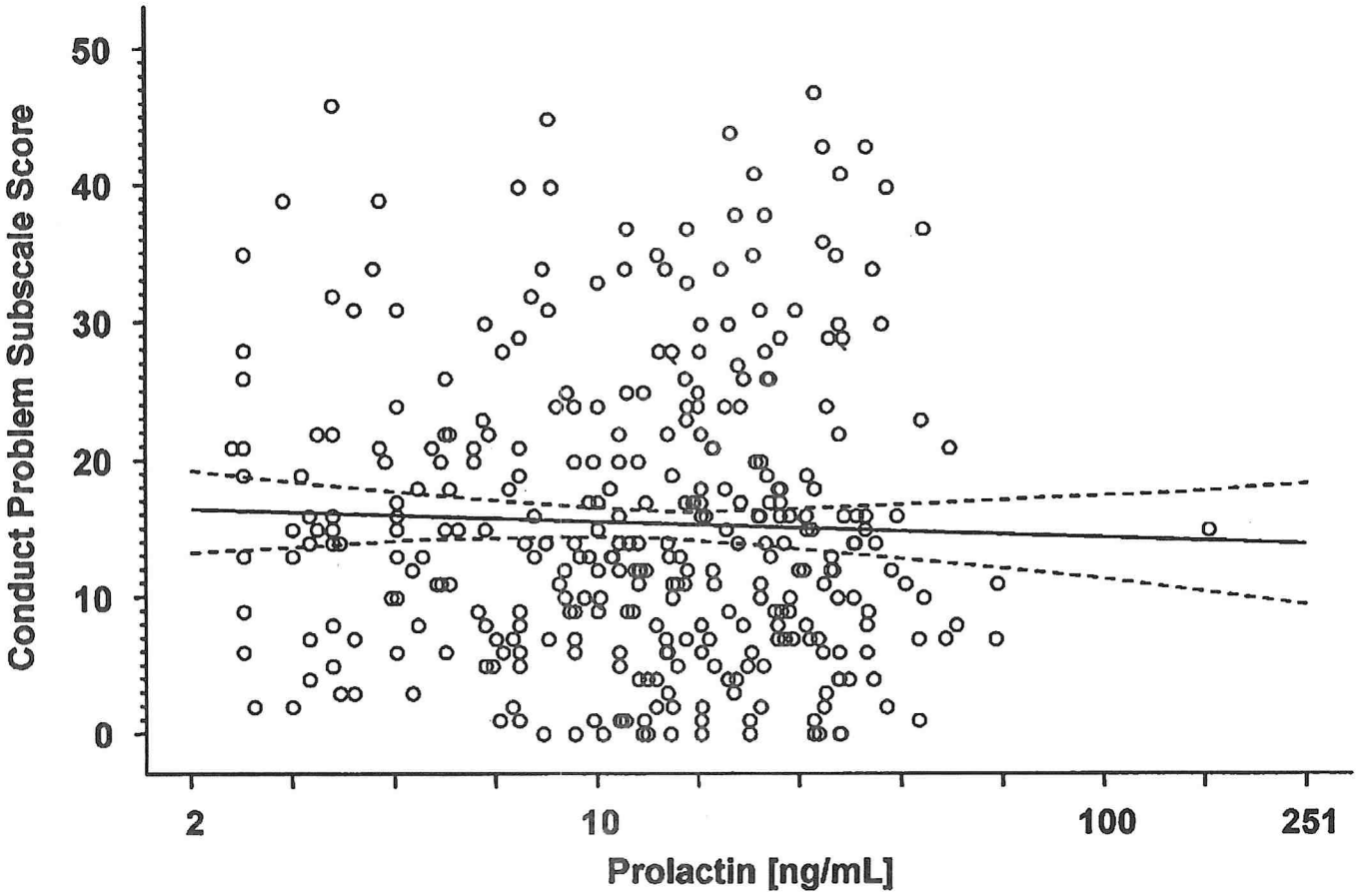
Weeks 4 to 7 (PA – as Observed)



·Data on file: Johnson & Johnson PRD, LLC

Conduct Problem Subscale Score vs Prolactin Levels

Weeks 40 to 48 (PA – as Observed)



*Data on file: Johnson & Johnson PRD, LLC

Correlation Between PRL Level and NCBRF Conduct Problem Subscale Score

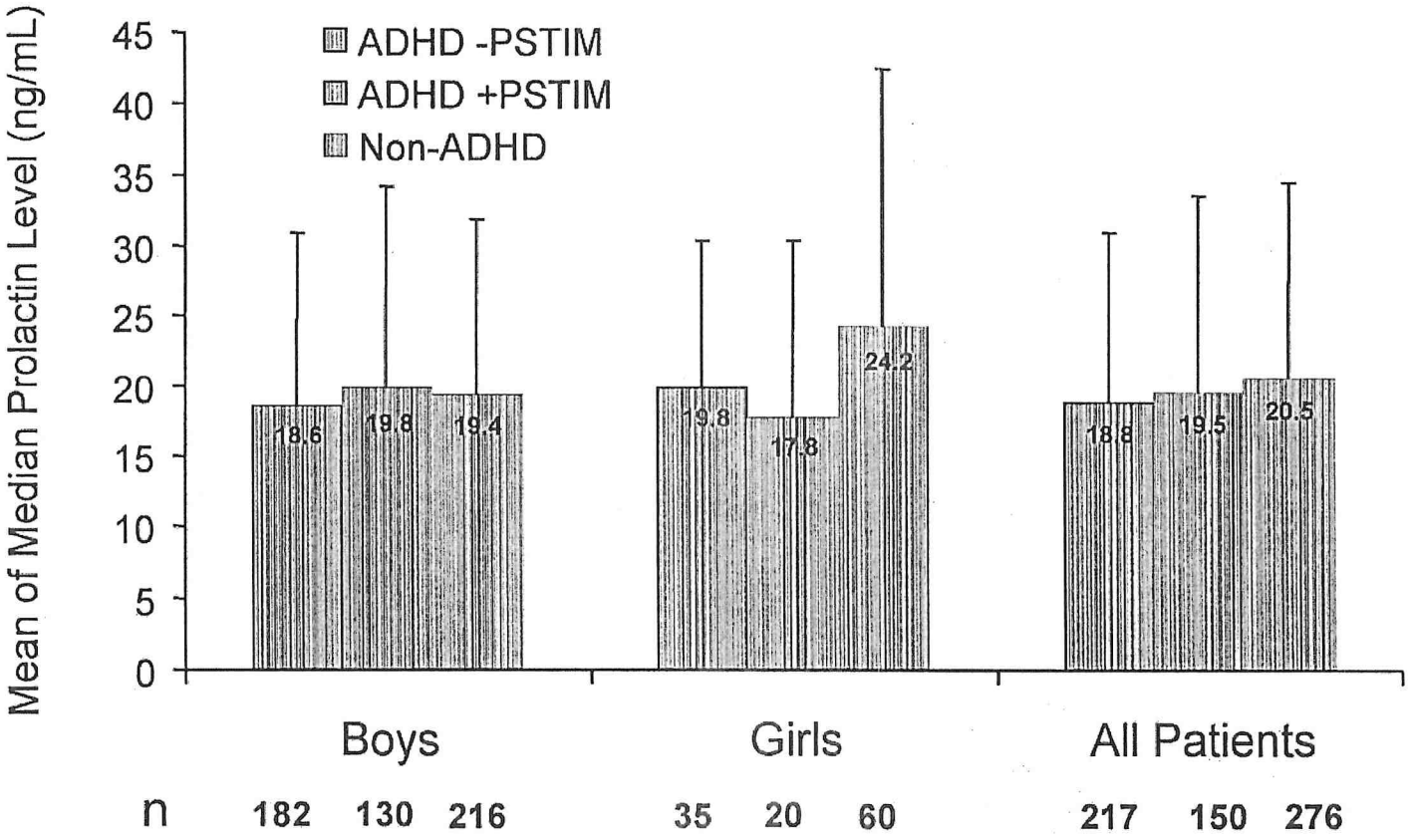
Exposure	n	Variance (Percent)*
Pre-dose	592	0.03
Weeks 4 to 7	547	0.93
Weeks 8 to 12	496	0.29
Weeks 16 to 24	438	0.19
Weeks 28 to 36	392	0.24
Weeks 40 to 48	355	0.14

***Percent of variation in subscale score that can be attributed to prolactin level; R^2 x 100**

Data on file: Johnson & Johnson PRD, LLC

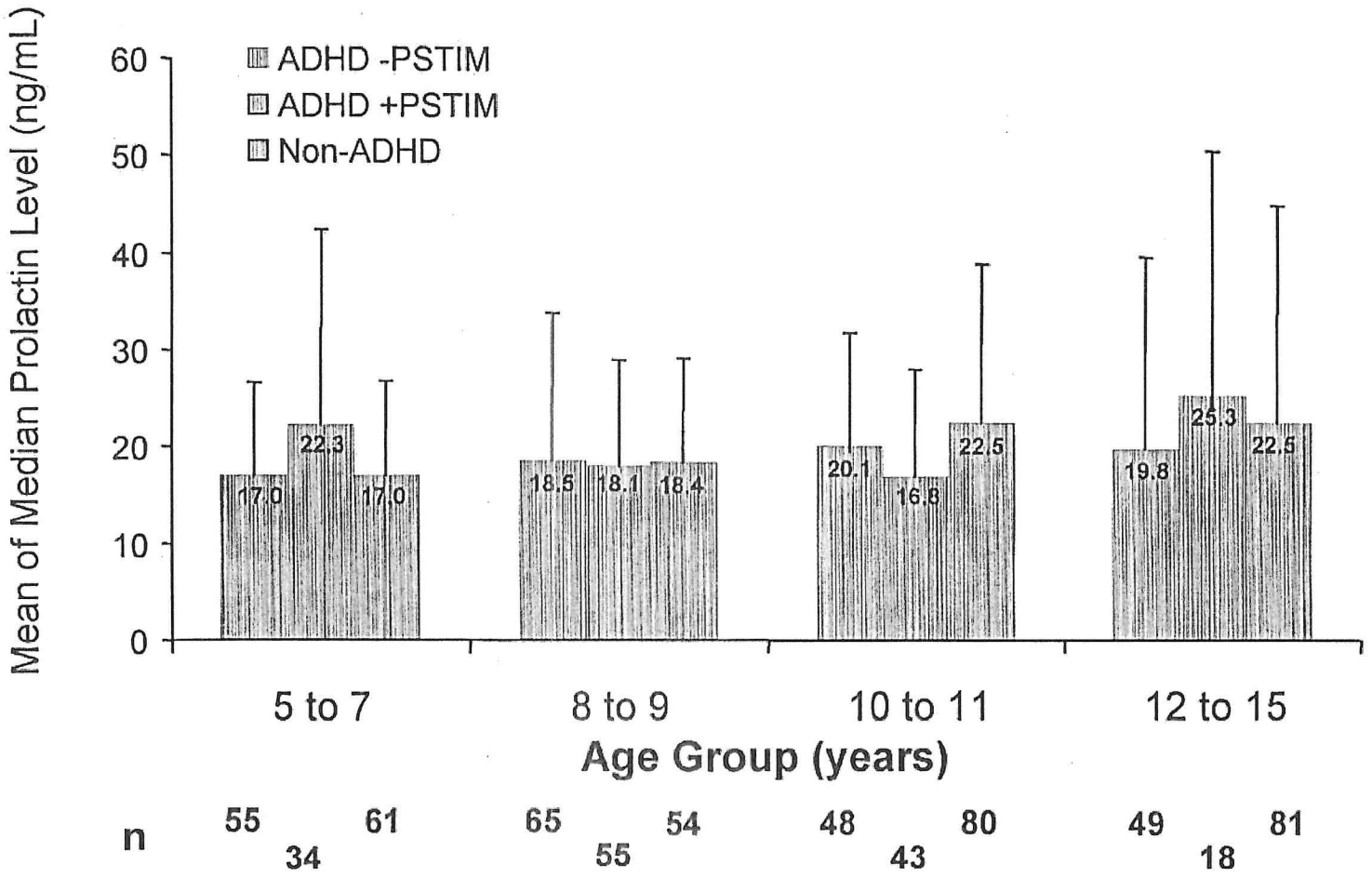
Comorbid ADHD
± Psychostimulants

PRL Level by ADHD Group



Data on file: Johnson & Johnson PRD, LLC

PRL Level by Age and ADHD Group: All Patients



Data on file: Johnson & Johnson PRD, LLC

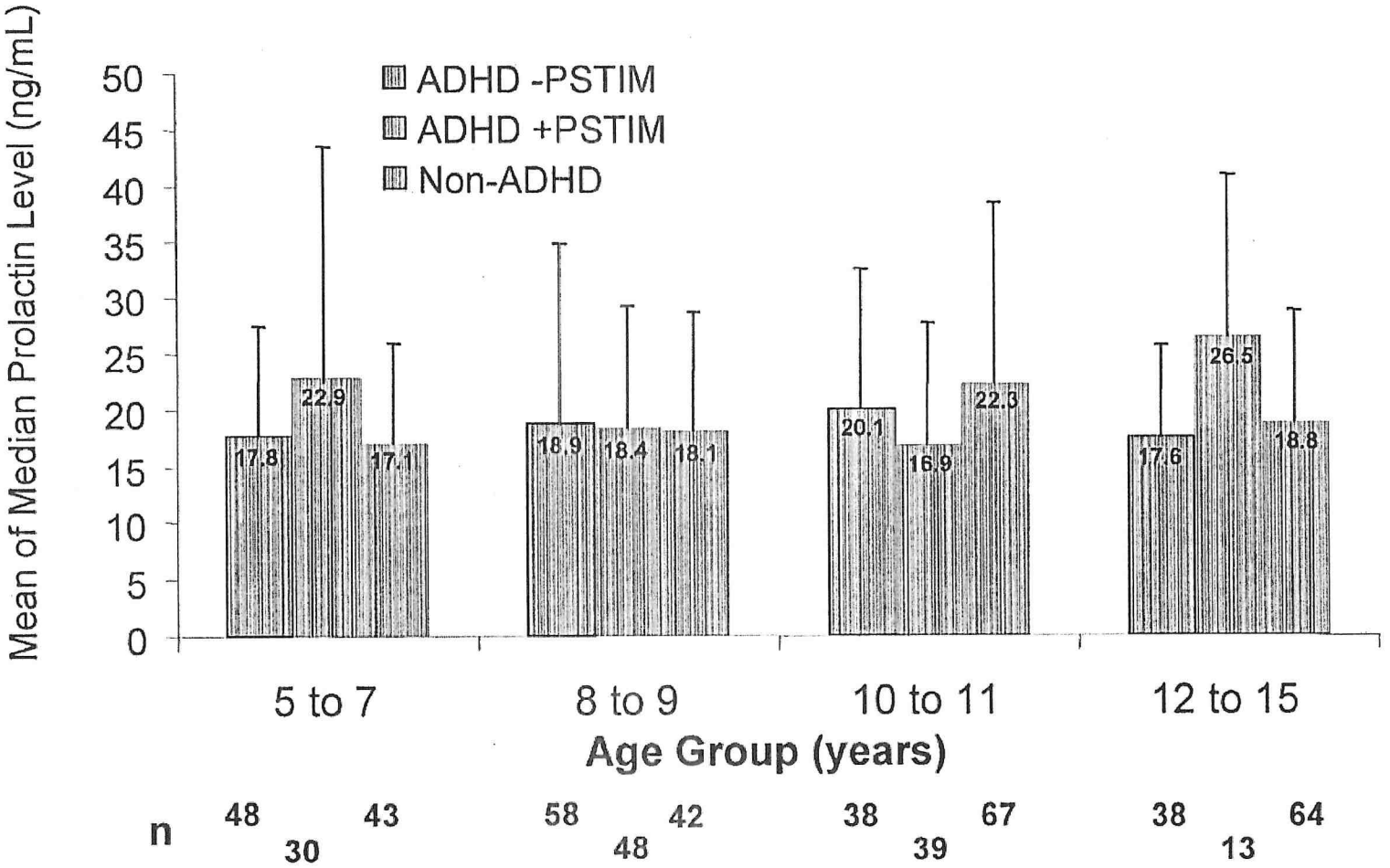
Analysis of Median Prolactin Level: Effect of ADHD Groups

- **Both genders**
- **All age groups**

Factor	*P*-values
Age group	0.001
Gender	0.70
Age group x gender interaction	0.05
ADHD groups	0.16
Age group x ADHD interaction	0.68
Gender x ADHD interaction	0.07
Age group x gender x ADHD interaction	0.61

'Data on file: Johnson & Johnson PRD, LLC

PRL Level by Age and ADHD Group in Boys



Data on file: Johnson & Johnson PRD, LLC

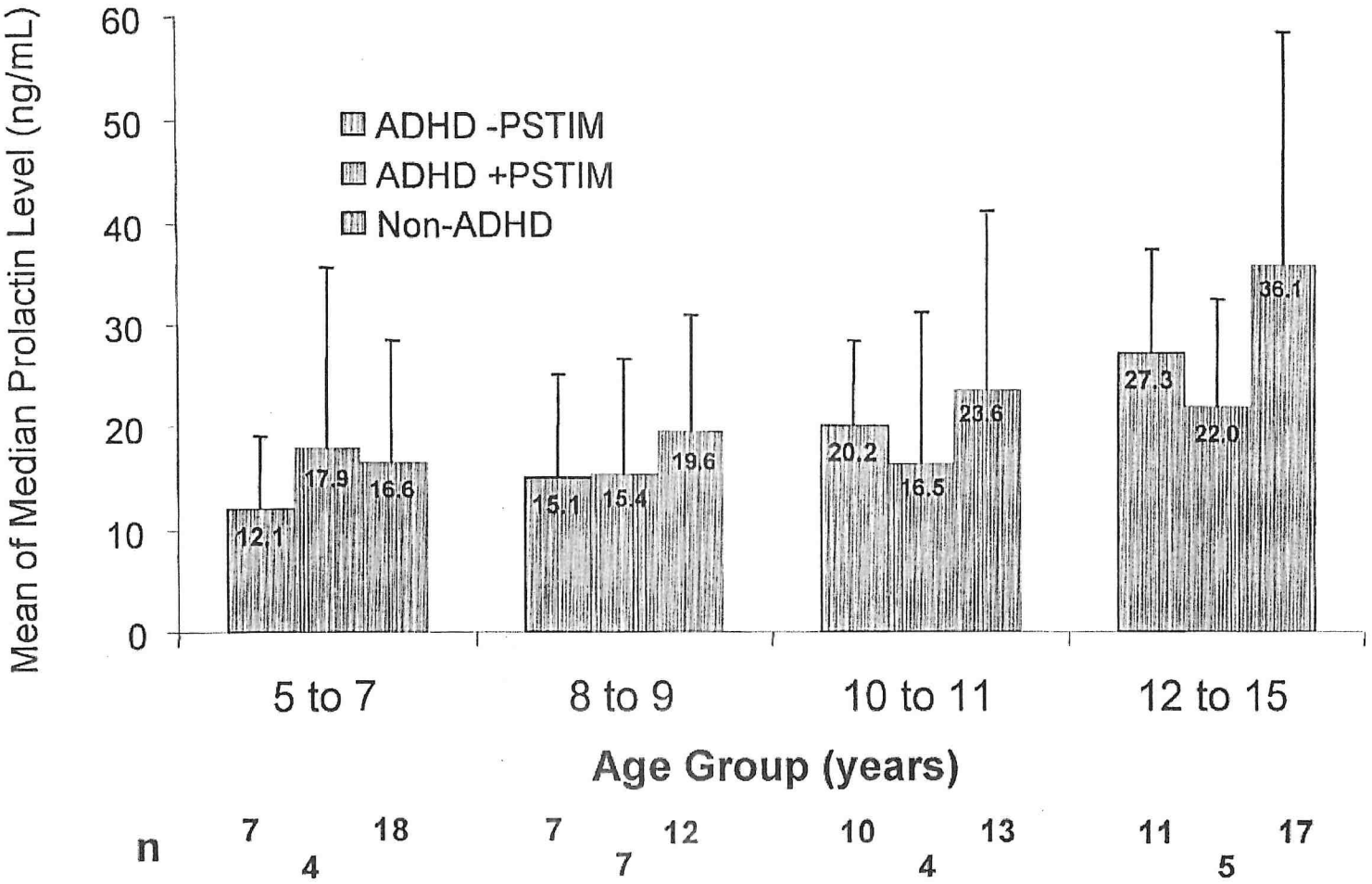
Analysis of Median Prolactin Level: Effect of ADHD Groups

- **Boys only**
- **All age groups**

Factor	*P*-values
Age group	0.57
ADHD groups	0.25
Age group x ADHD interaction	0.05

Data on file: Johnson & Johnson PRD, LLC

PRL Level by Age and ADHD Group in Girls



Data on file: Johnson & Johnson PRD, LLC

Analysis of Median Prolactin Level: Effect of ADHD Groups

- **Girls only**
- **All age groups**

Factor	*P*-values
Age group	0.01
ADHD groups	0.13
Age group x ADHD interaction	0.88

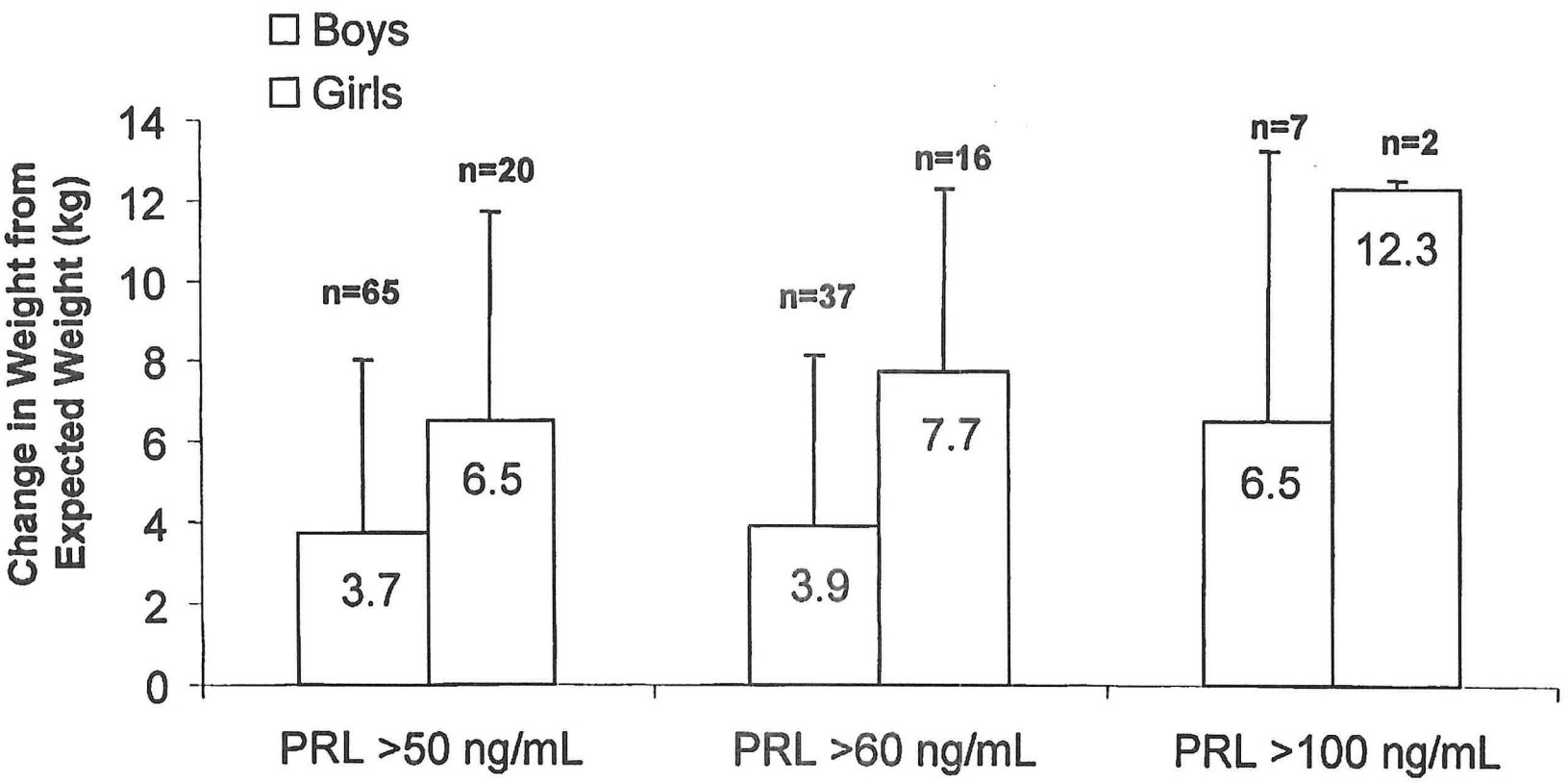
Data on file: Johnson & Johnson PRD, LLC

Summary

- No association of PRL level and:
  - SHAP
  - Motor effects
  - Efficacy
  - ADHD and PSTIM

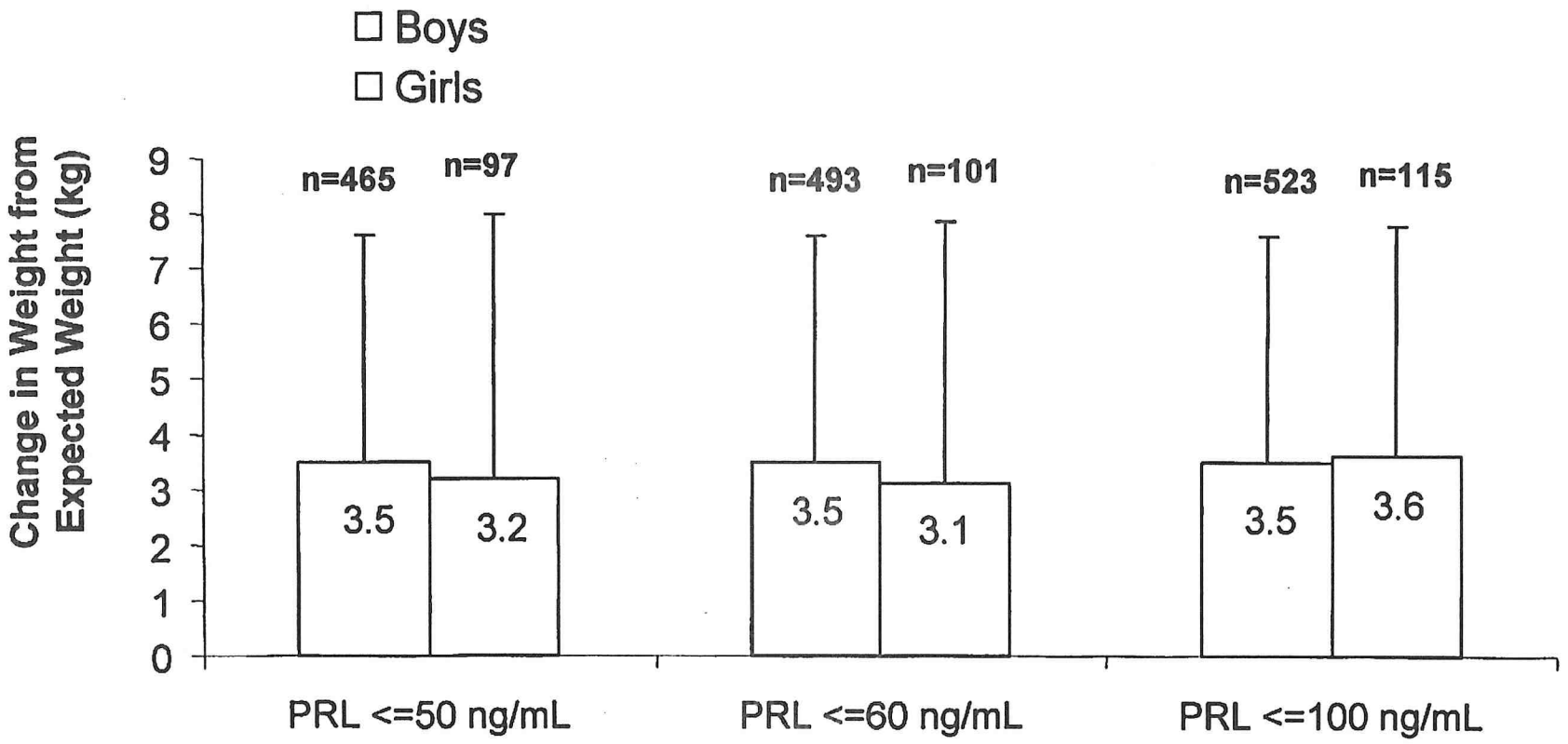
Back-up Slides

Change in Weight at Endpoint From Expected Weight



*Data on file: Johnson & Johnson PRD, LLC

Change in Weight at Endpoint From Expected Weight



·Data on file: Johnson & Johnson PRD, LLC

Analysis of Change in Weight at Endpoint From Expected Weight: Effect of Prolactin

- ≤60 vs >60
- Both genders
- All age groups

Factor	*P*-values
Age group	0.06
Gender	0.12
Age group x gender interaction	0.79
PRL	0.01
Age group x PRL interaction	0.63
Gender x PRL interaction	0.05
Age group x gender x PRL interaction	0.86

'Data on file: Johnson & Johnson PRD, LLC

Analysis of Change in Weight at Endpoint From Expected Weight: Effect of Prolactin

- ≤60 vs >60
- Boys only
- All age groups

Factor	*P*-values
Age group	0.23
PRL	0.47
Age group x PRL interaction	0.98

*Data on file: Johnson & Johnson PRD, LLC

Analysis of Change in Weight at Endpoint From Expected Weight: Effect of Prolactin

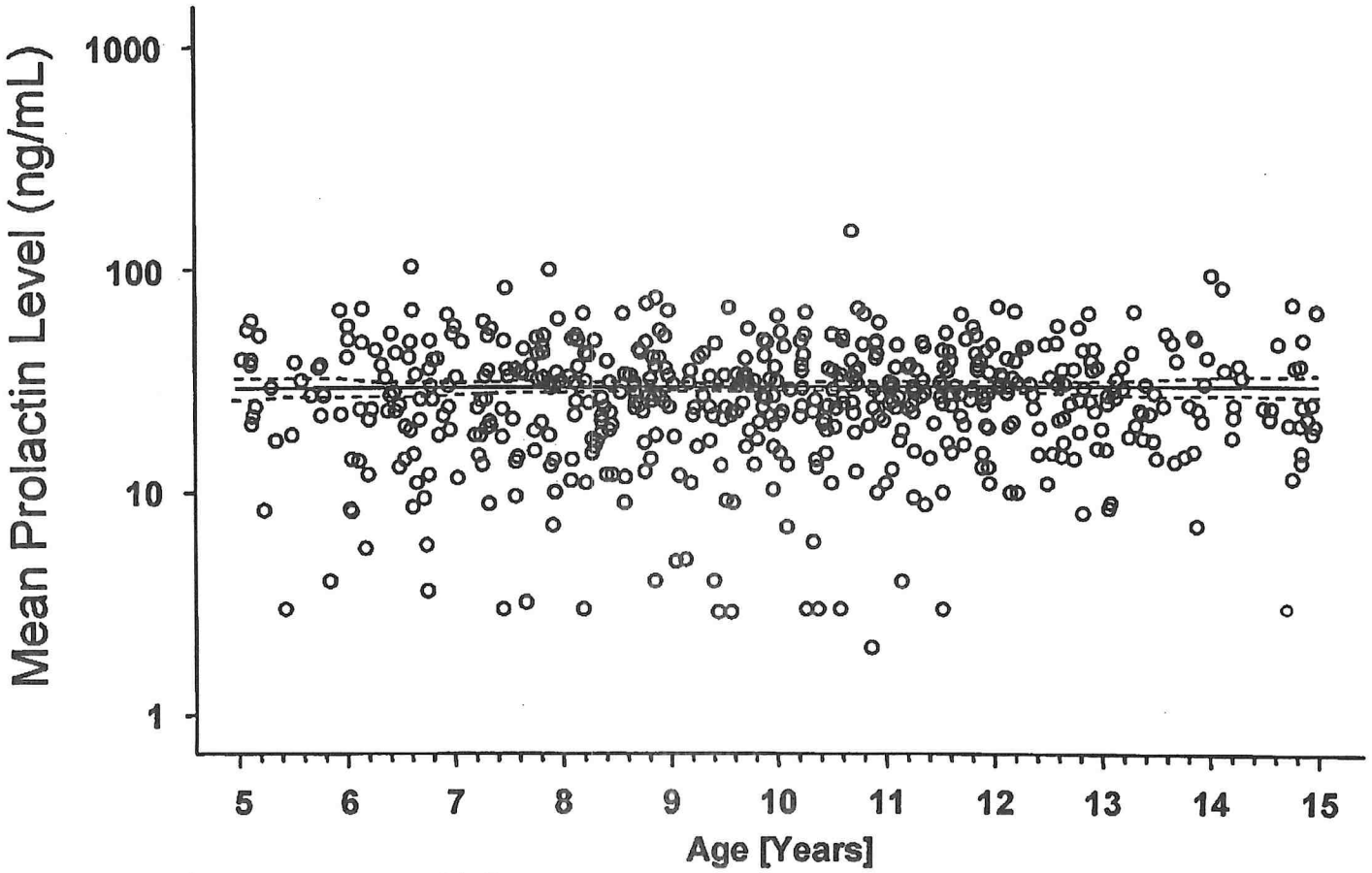
- ≤60 vs >60
- Girls only
- All age groups

Factor	*P*-values
Age group	0.35
PRL	0.02
Age group x PRL interaction	0.71

•Data on file: Johnson & Johnson PRD, LLC

Prolactin Levels vs Age

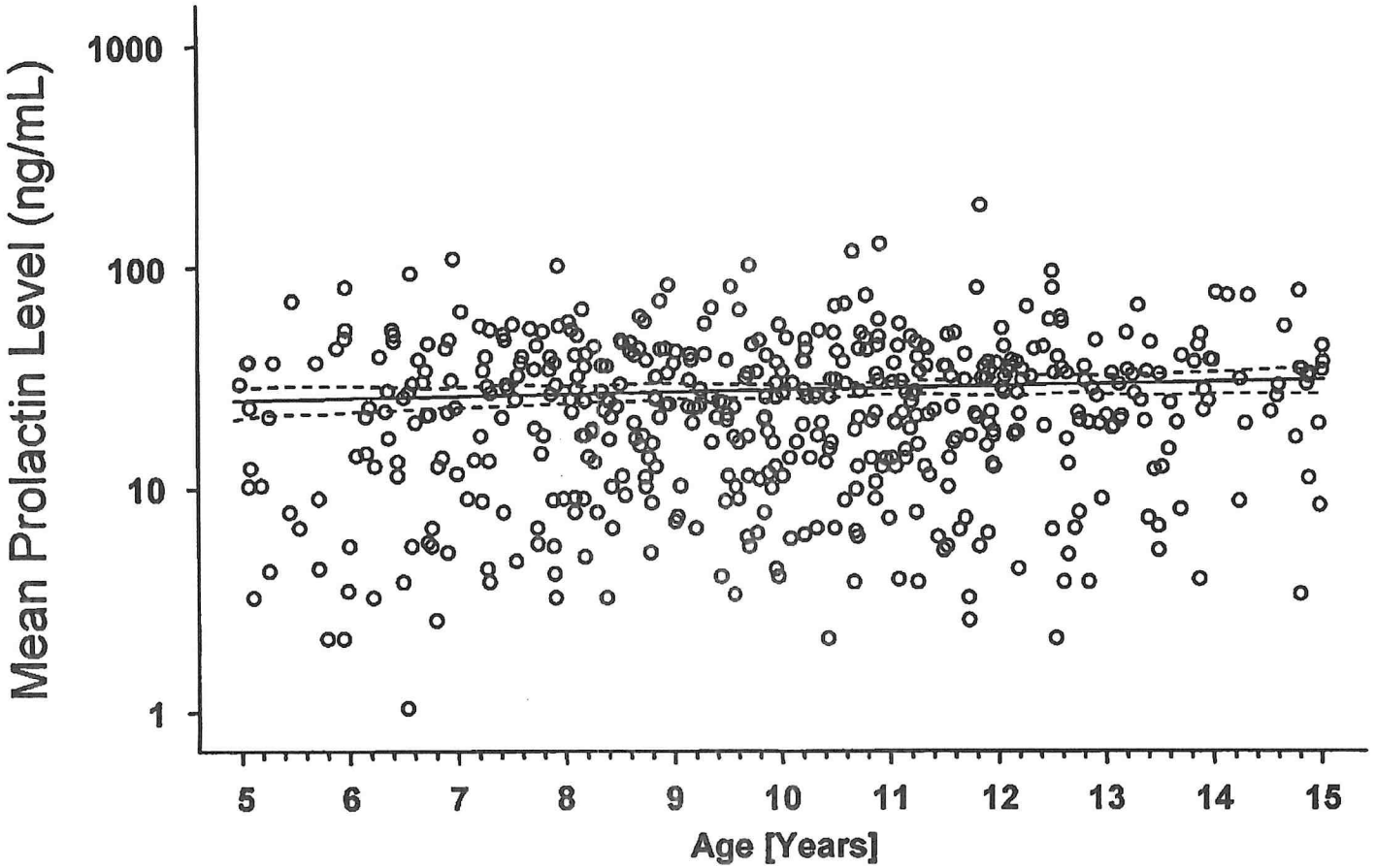
Weeks 4 to 7 (PA – as Observed): Log Scale



- Data on file: Johnson & Johnson PRD, LLC

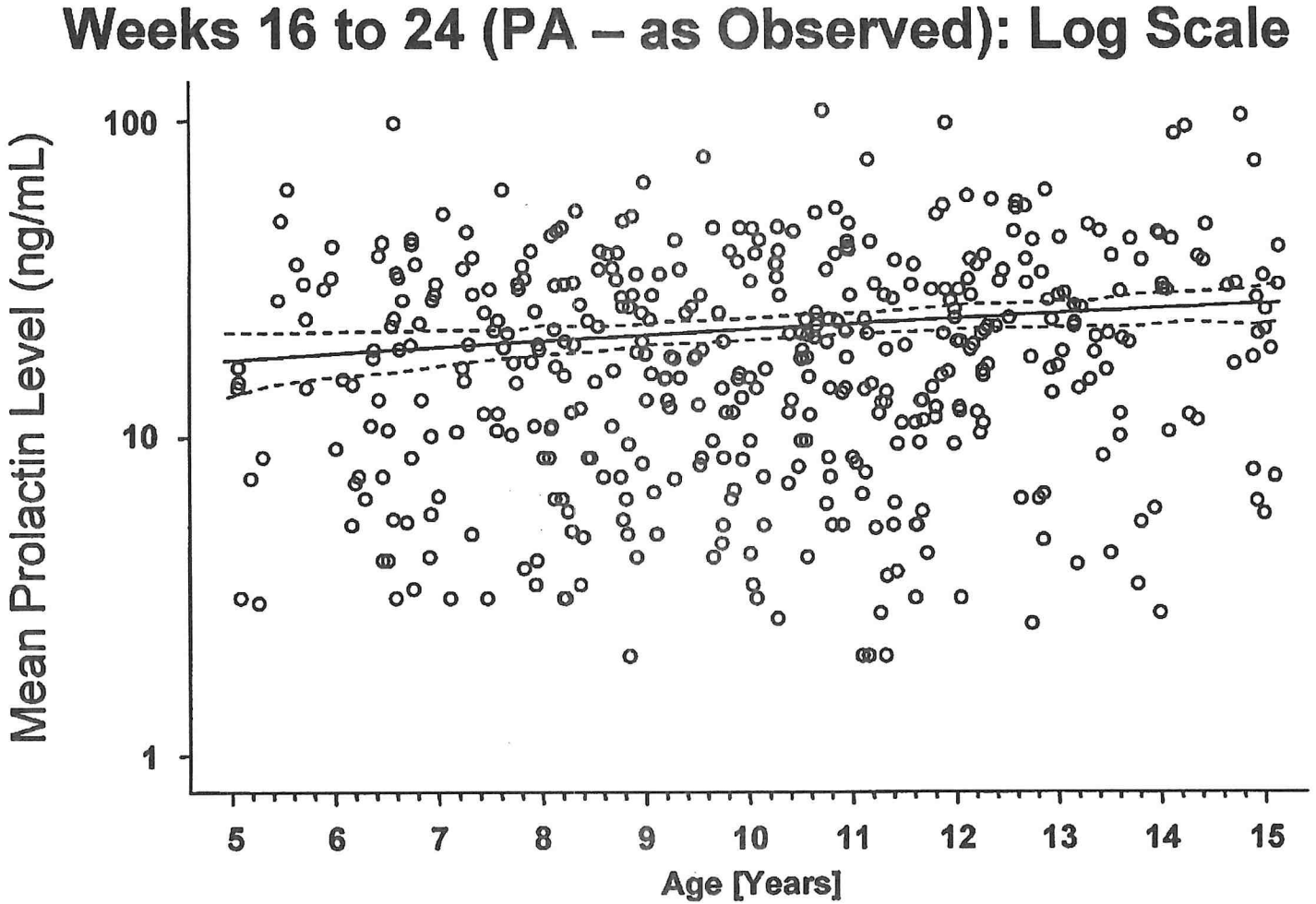
Prolactin Levels vs Age

Weeks 8 to 12 (PA – as Observed): Log Scale



*Data on file: Johnson & Johnson PRD, LLC

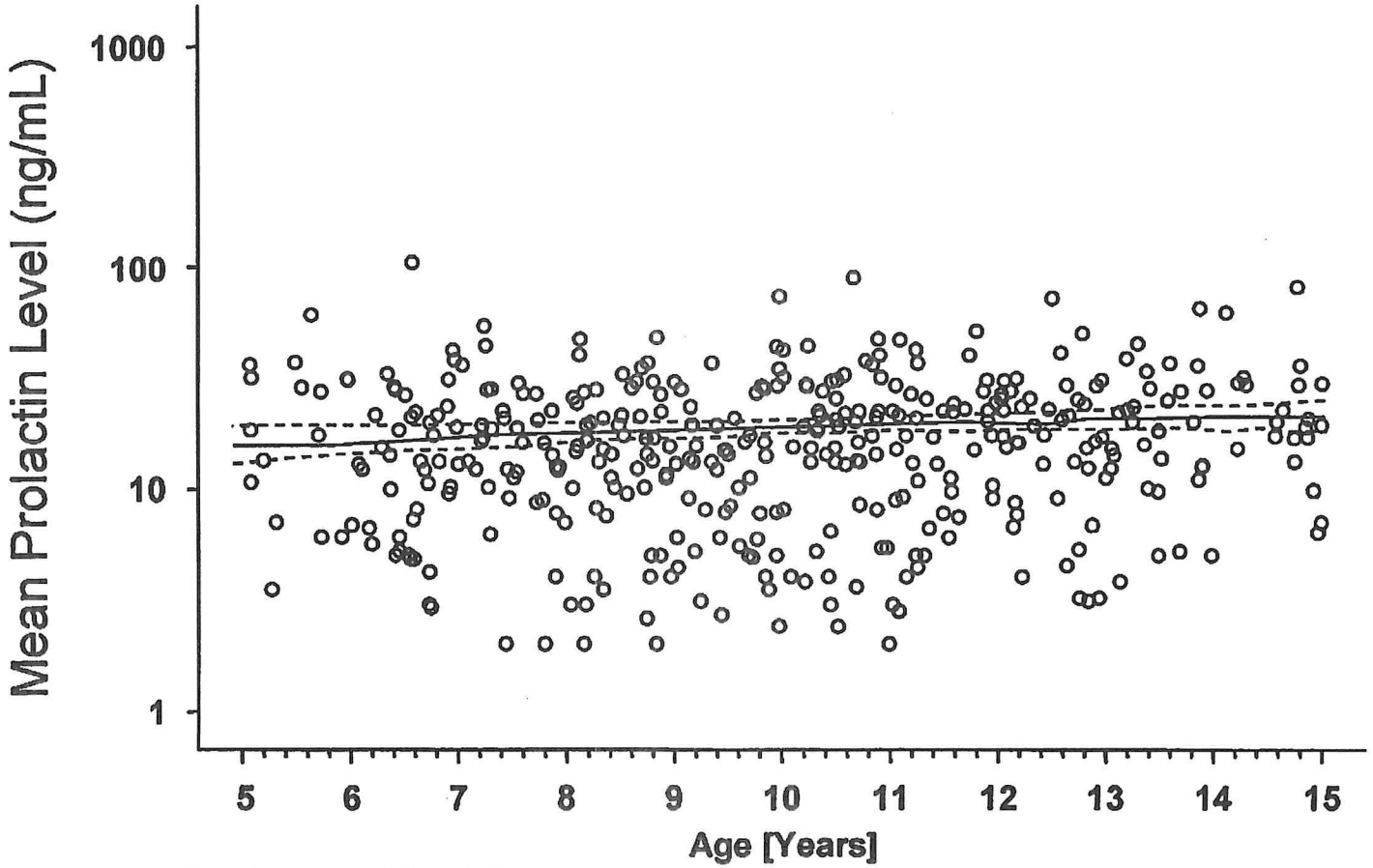
Prolactin Levels vs Age



[9]Data on file: Johnson & Johnson PRD, LLC

Prolactin Levels vs Age

Weeks 28 to 36 (PA – as Observed): Log Scale



Data on file: Johnson & Johnson PRD, LLC