To: Pillai, Prita[prita_pillai@merck.com]
From: Desmond, Ruth V.
Sent: Tue 8/8/2000 11:40:10 AM
Importance: Normal
Subject: FW: Overheads for CDOC 8/2/00
CDOC800.ppt

Hi Prita,
These are the slides Keith used at CDOC last week. It all cleared that committee very cleanly.
Ruth

From: Kaufman, Keith D.
Sent: Tuesday, August 01, 2000 1:28 PM
To: Greene, Douglas Dr.; Nies, Alan S.; Slater, Eve; Gertz, Barry J.; Margolskee, Dorothy
Cc: Merritt, Charlotte B.; Goodrow, Tamra L.; Stoner, Elizabeth; Blois, David W.; Wang, Cynthia; White-Guay, Brian; Desmond, Ruth V.; Casola, Tom; Howes, Paul G.; Taglieber, U.
Subject: Overheads for CDOC 8/2/00

Attached are the presentation slides for the 8/2 CDOC for the following item:

PROPECIA - 5-Year Phase III Pivotal Data and EU Regulatory Strategy,
Dr. Keith Kaufman and Ms. Charlotte Merritt

PROPECIA

5-Year End-of-Study Phase III Controlled Data

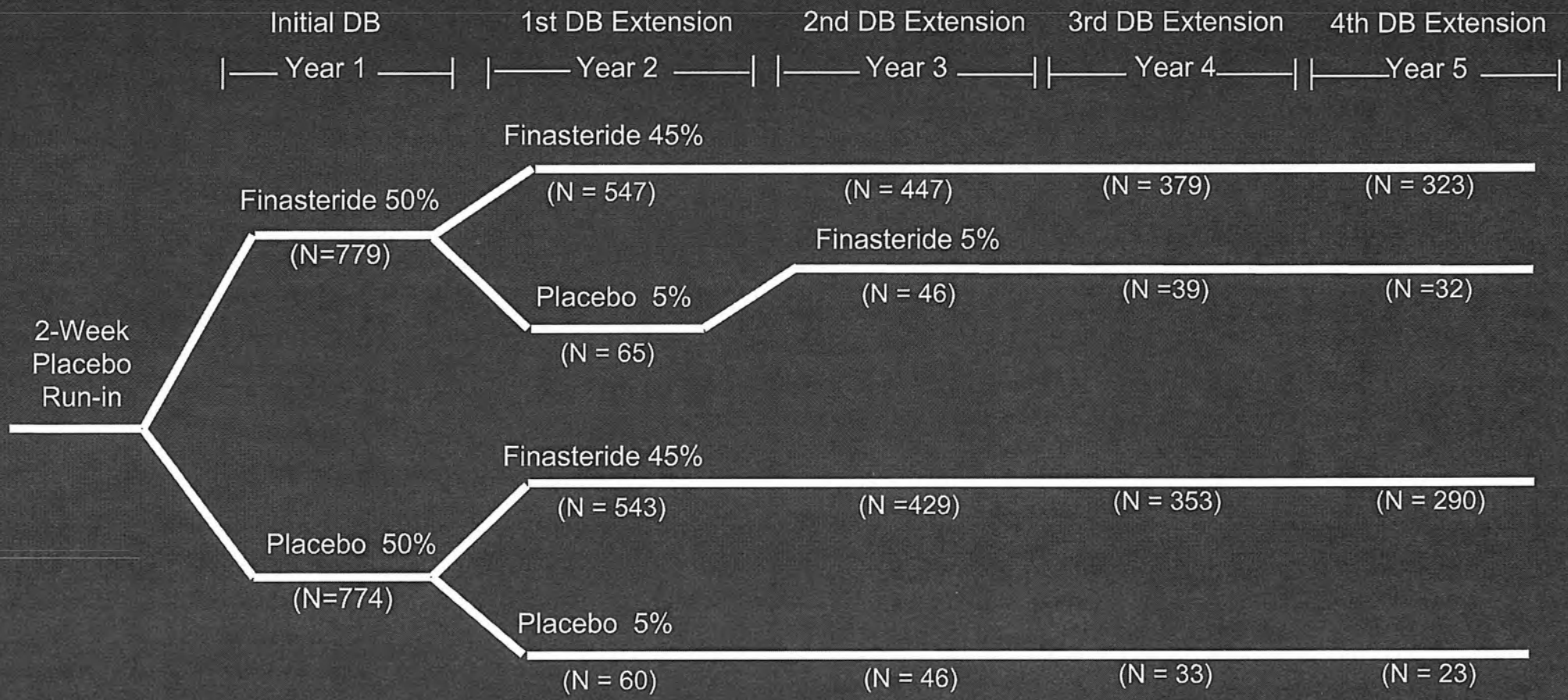
PROPECIA: 5-Year Phase III Controlled Data

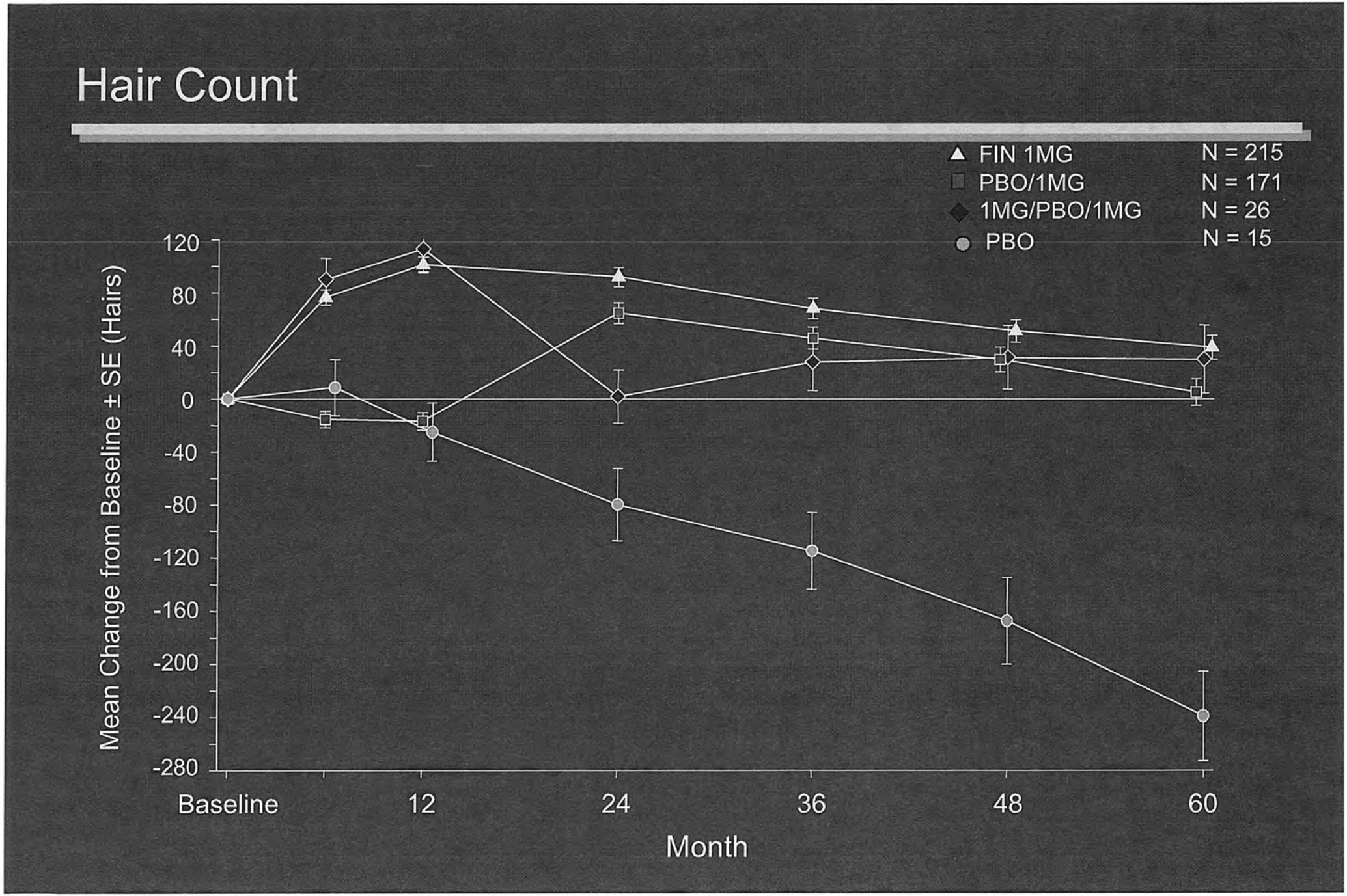
Background

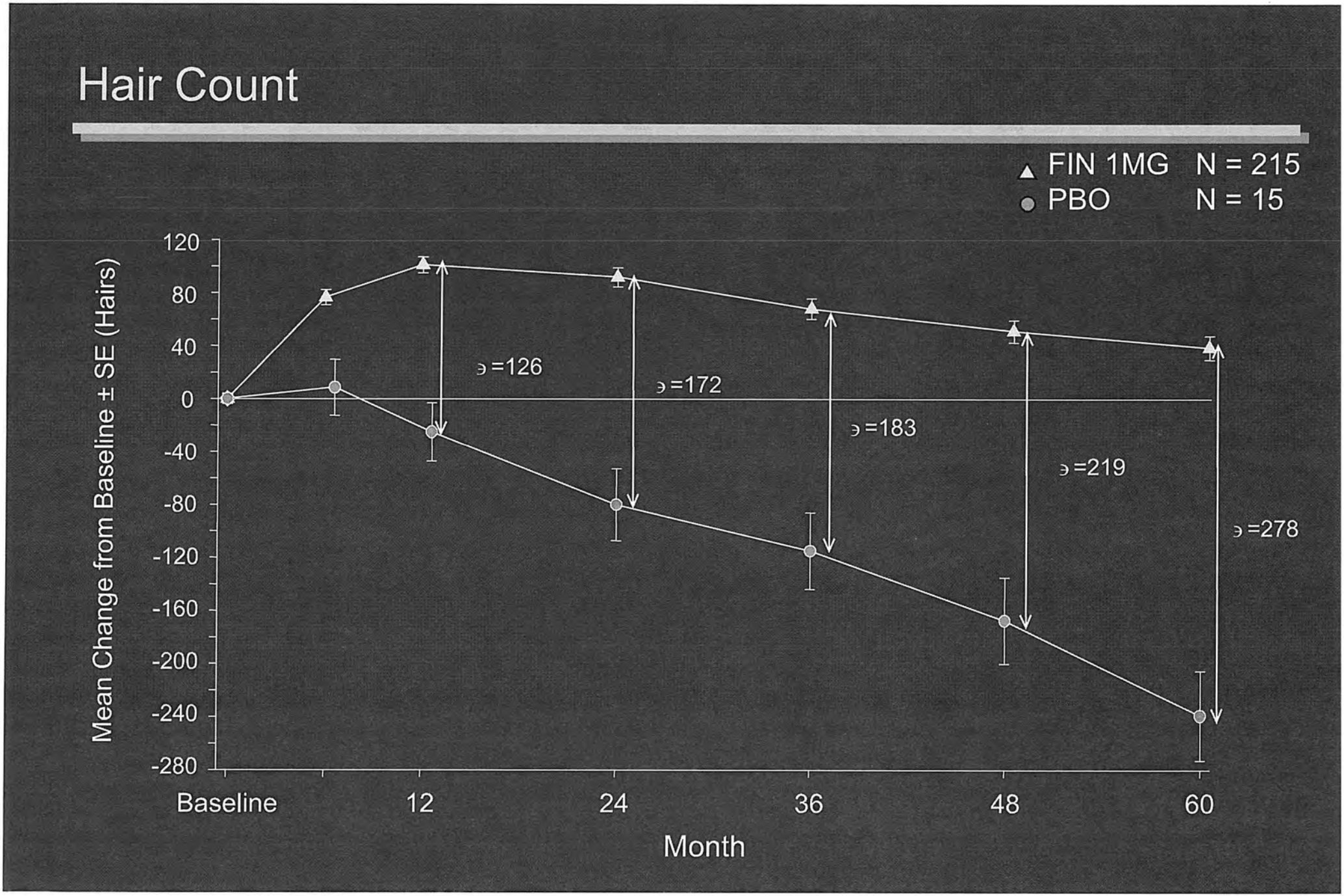
* DEC94: Initiated Phase III studies (1-yr + 1-yr controlled extensions)
* DEC96: Filed WMA (1-yr Phase III data)
* AUG97: Updated application w/2-yr data
* DEC97: US approval w/2-yr data in label; *5-yr Phase IV commitment*
* JUL98: Filed MR procedure in EU w/ 2-yr data
* SEP98: EU approval (n=8; withdrawal=6 w/long-term S/E concerns)
* AUG99: CDOC review of 4-yr Phase III data
* MAY00: Phase III controlled extensions complete (5-yr data)

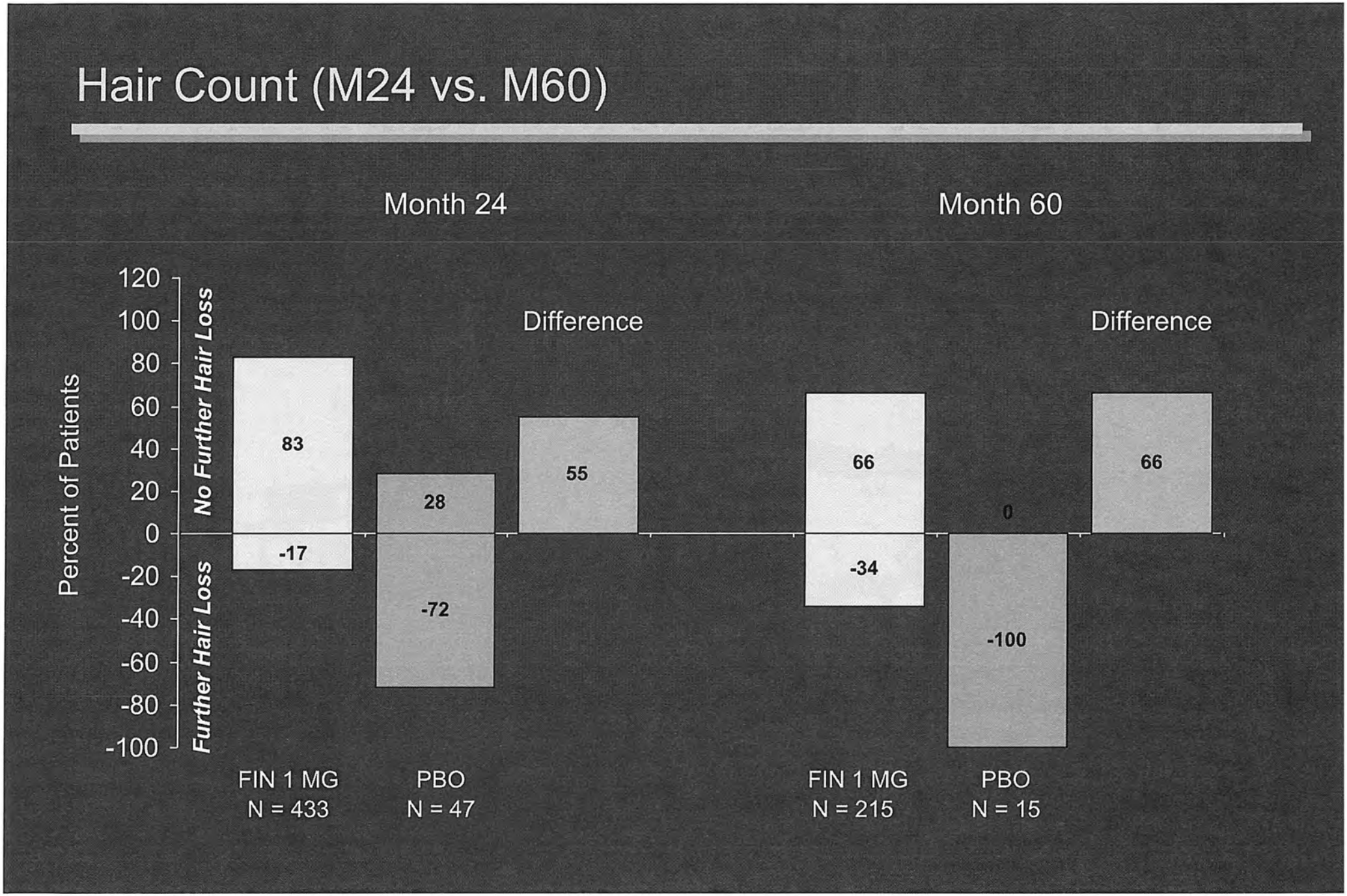
Phase III Pivotal Studies

Study Design

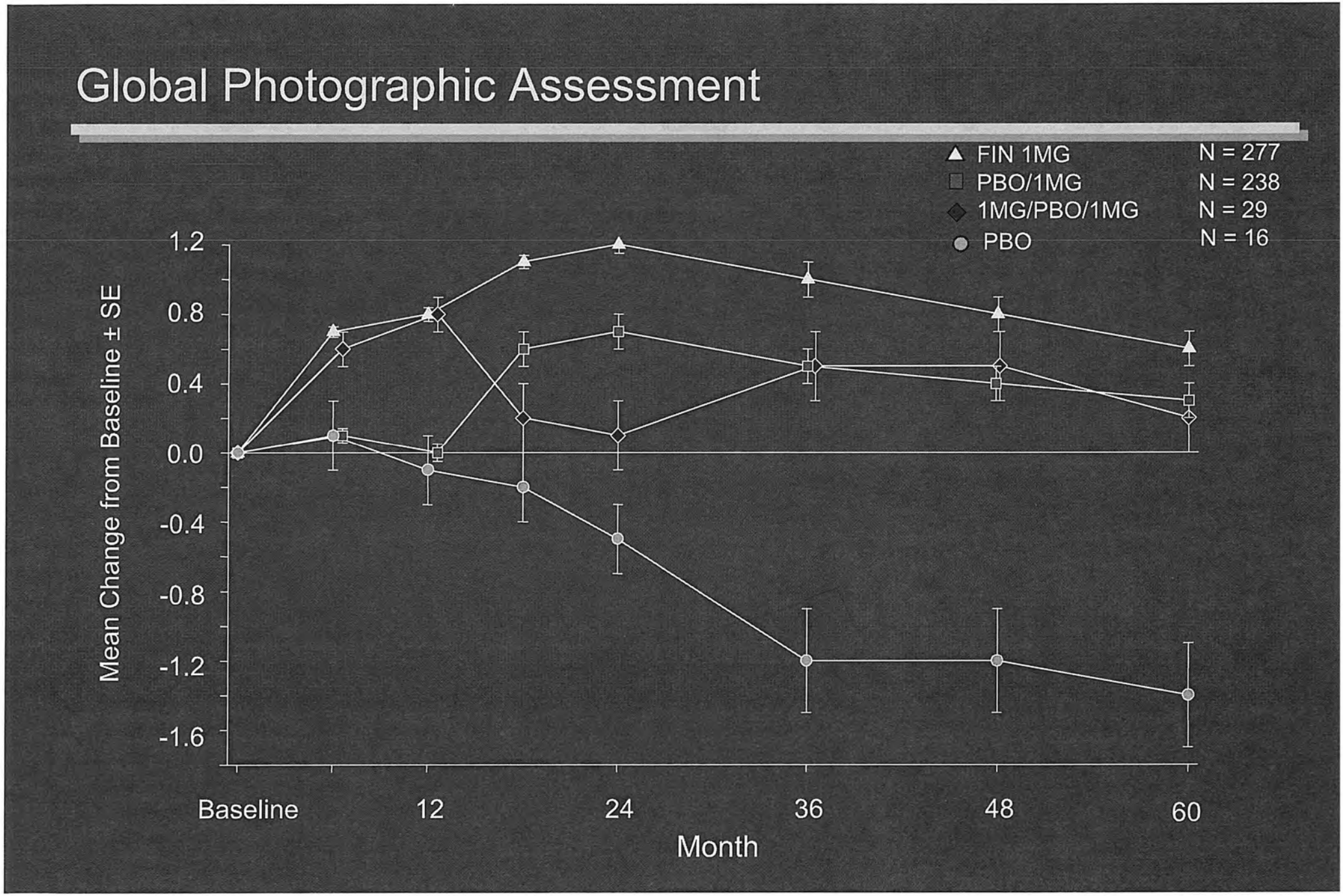


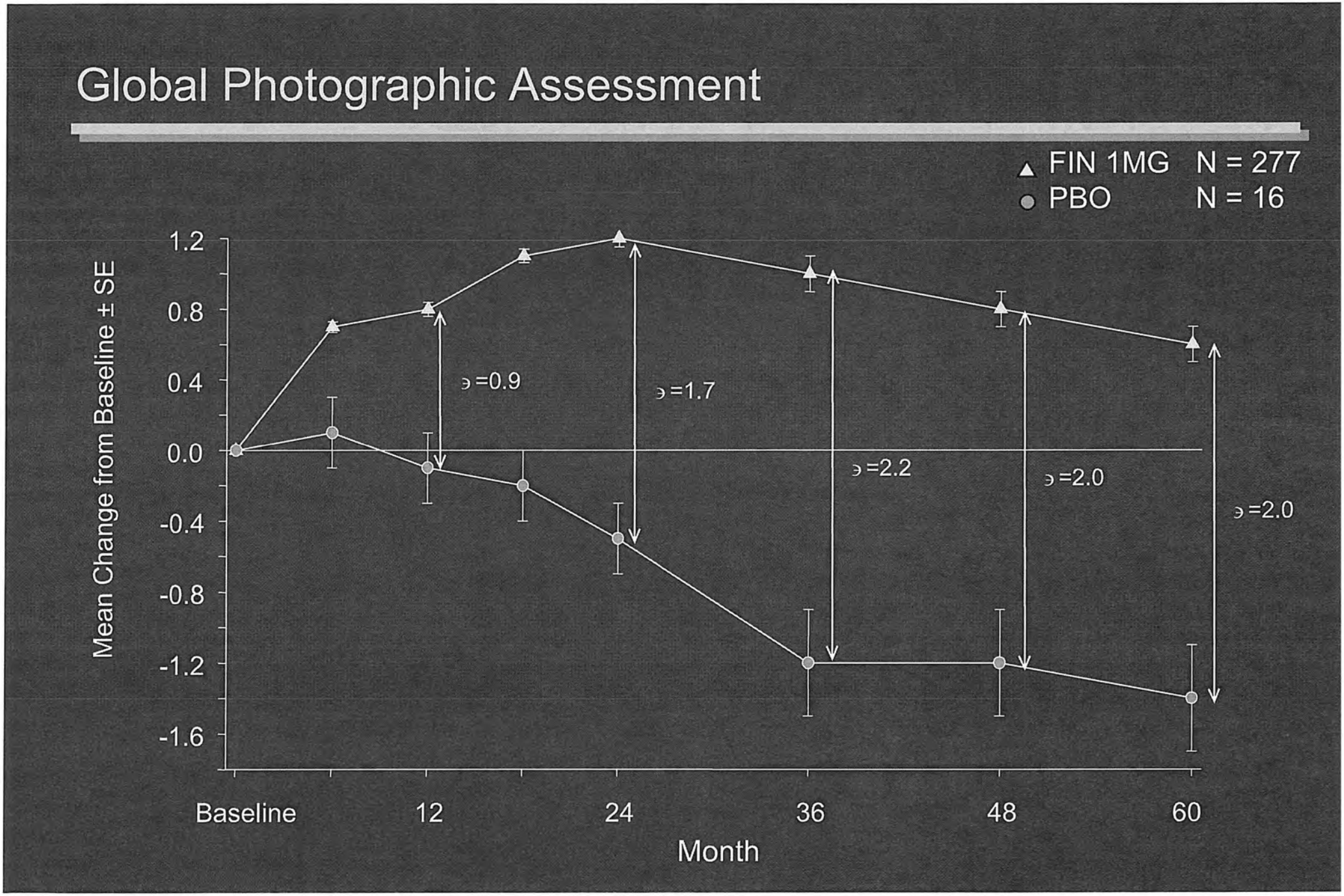

Hair Count
FIN 1MG
PBO/1MG
1MG/PBO/1MG
PBO
N = 215
N = 171
N = 26
N = 15
Mean Change from Baseline ± SE (Hairs)
120
80
40
0
-40
-80
-120
-160
-200
-240
-280
Baseline
12
24
36
48
60
Month

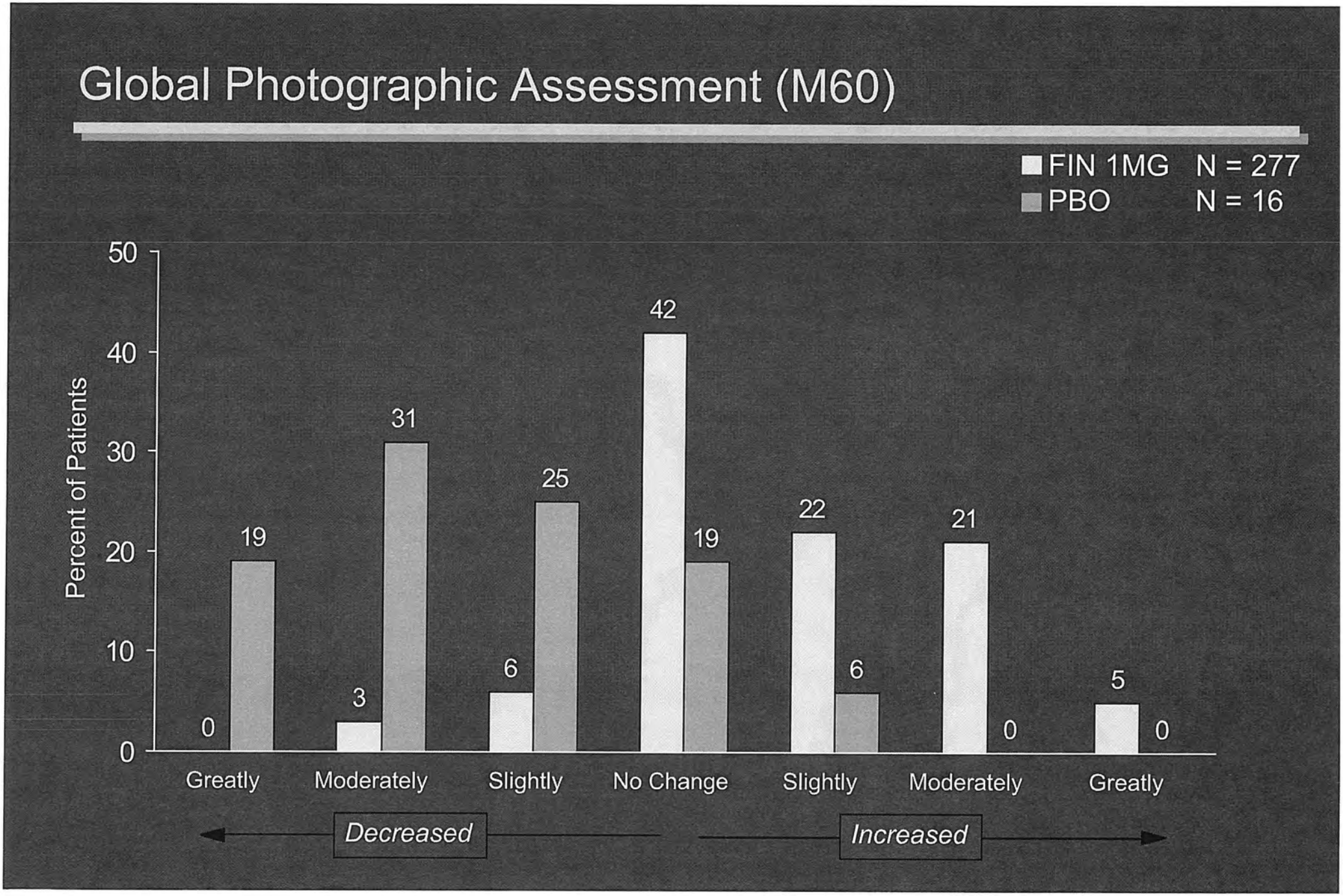

Hair Count
FIN 1MG N = 215
PBO N = 15
Mean Change from Baseline ± SE (Hairs)
120
80
40
0
-40
-80
-120
-160
-200
-240
-280
Baseline
12
24
36
48
60
Month
∋ =126
∋ =172
∋ =183
∋ =219
∋ =278


Hair Count (M24 vs. M60)
Month 24
Month 60
Percent of Patients
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
No Further Hair Loss
Further Hair Loss
Difference
Difference
83
-17
28
-72
55
66
-34
0
-100
66
FIN 1 MG
N = 433
PBO
N = 47
FIN 1 MG
N = 215
PBO
N = 15

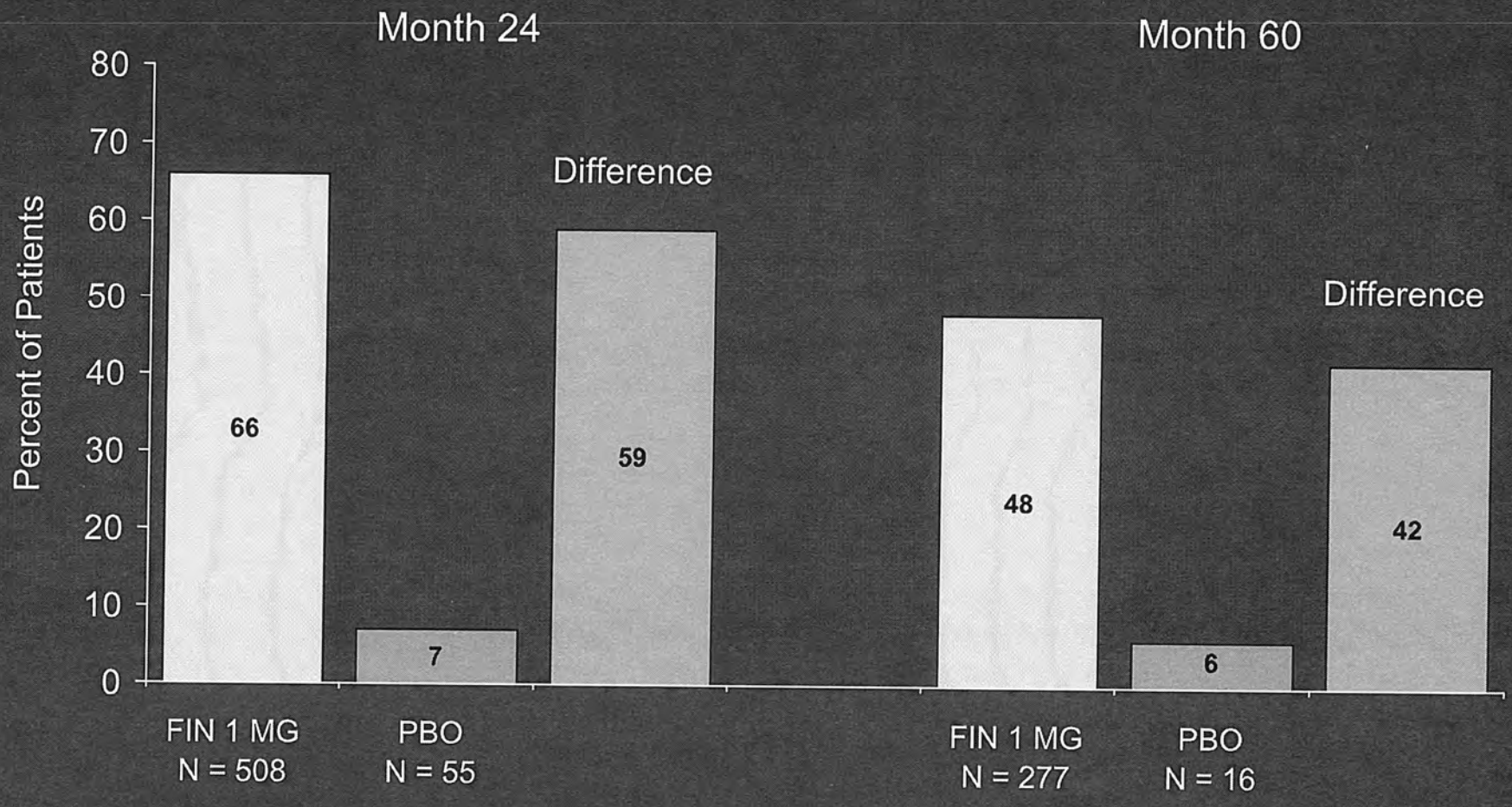
Global Photographic Assessment

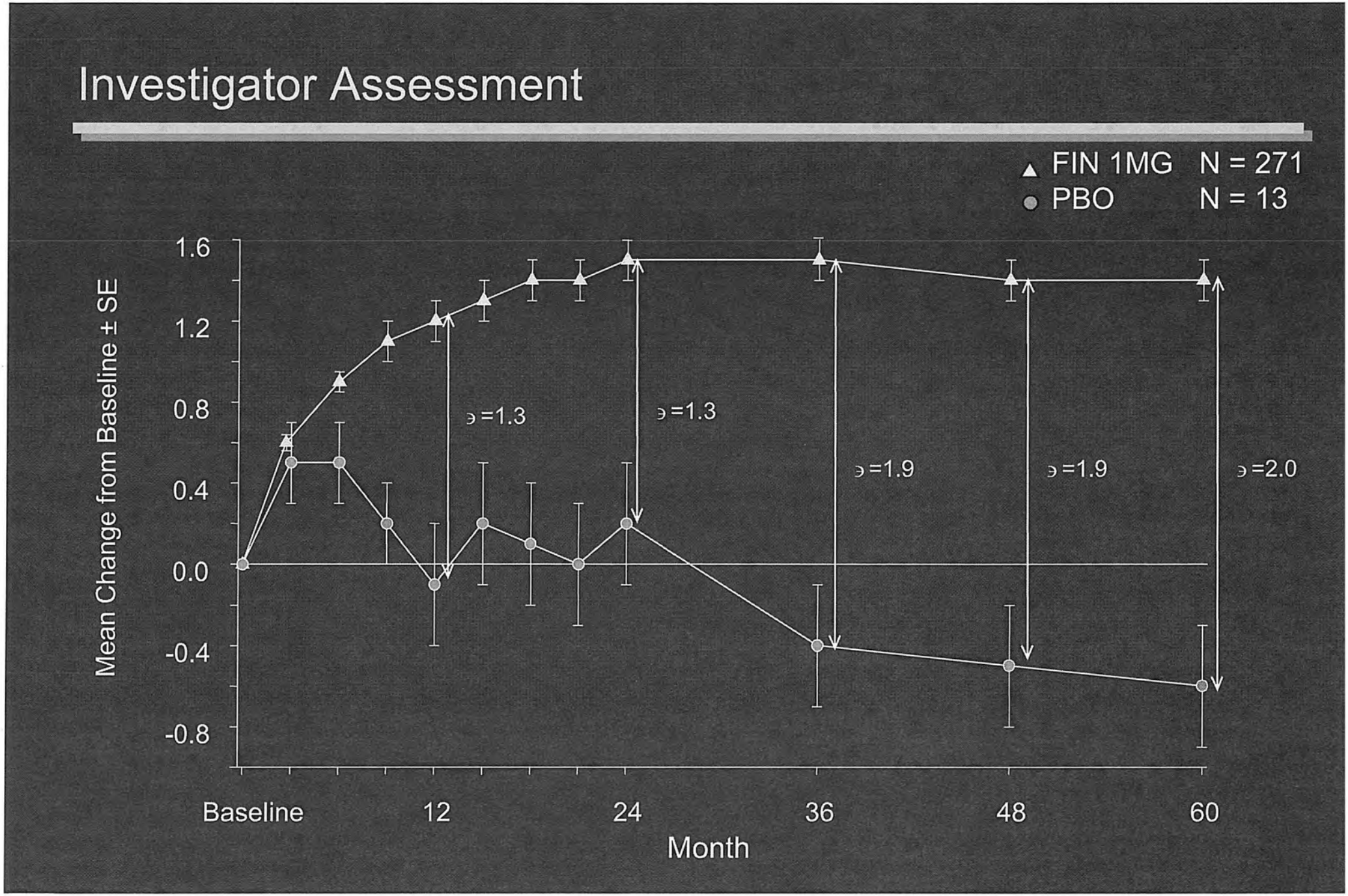


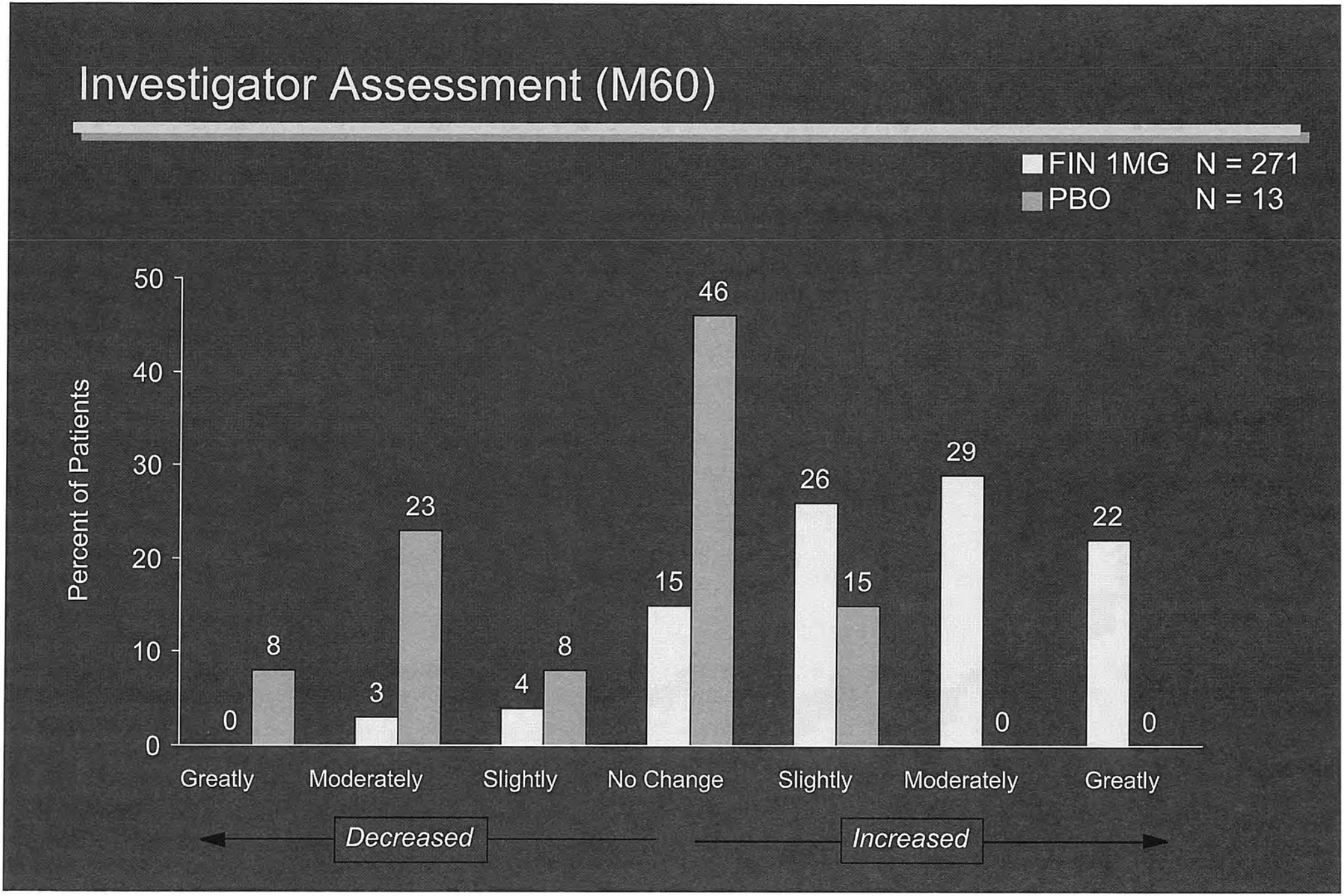

Global Photographic Assessment
FIN 1MG N = 277
PBO N = 16
Mean Change from Baseline ± SE
1.2
0.8
0.4
0.0
-0.4
-0.8
-1.2
-1.6
ɔ =0.9
ɔ =1.7
ɔ =2.2
ɔ =2.0
ɔ =2.0
Baseline
12
24
36
48
60
Month


Global Photographic Assessment (M60)
FIN 1MG N = 277
PBO N = 16
Percent of Patients
50
40
30
20
10
0
0
19
3
31
6
25
42
19
22
6
21
0
5
0
Greatly
Moderately
Slightly
No Change
Slightly
Moderately
Greatly
Decreased
Increased

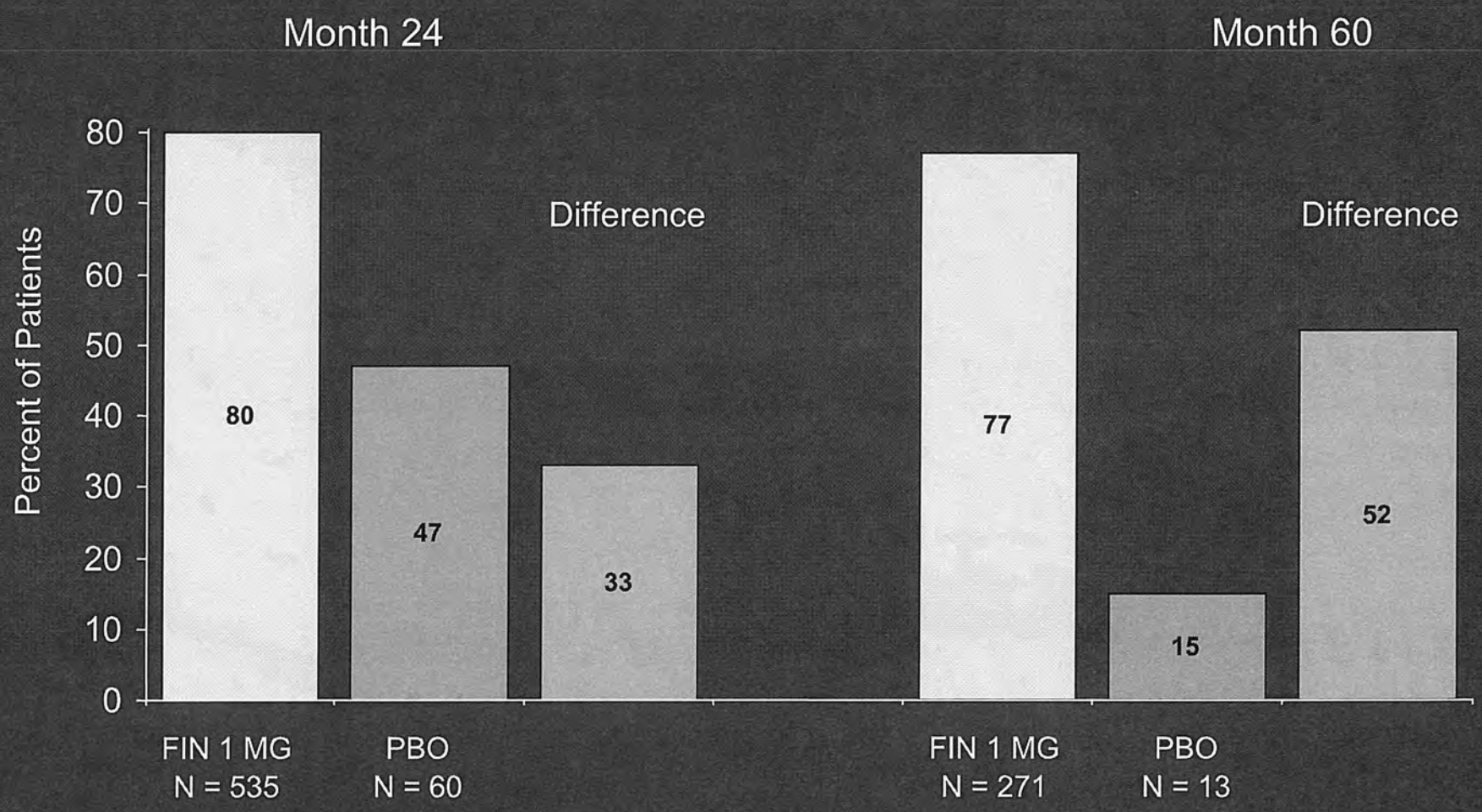
Global Photographic Assessment (M24 vs. M60)

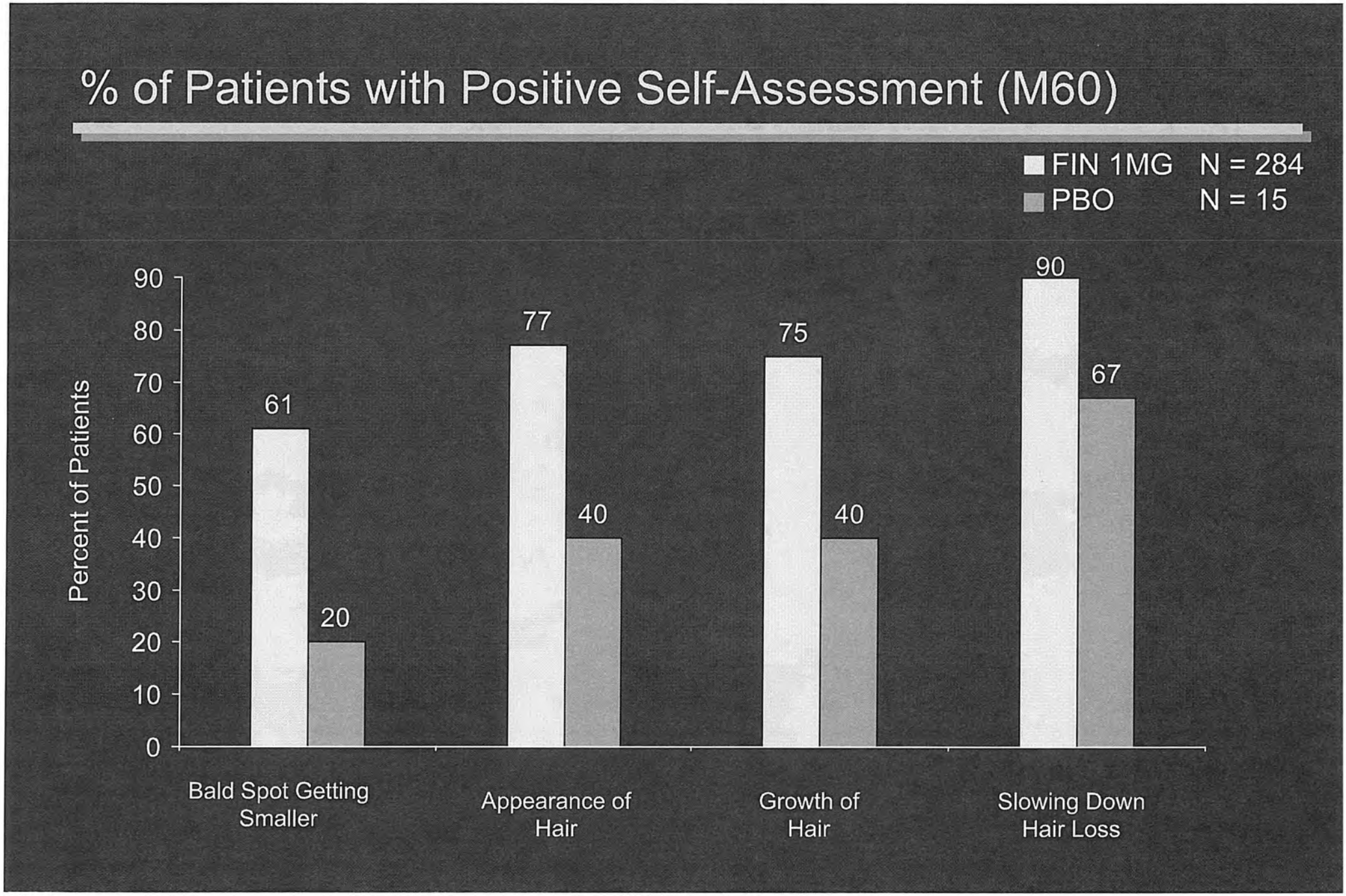


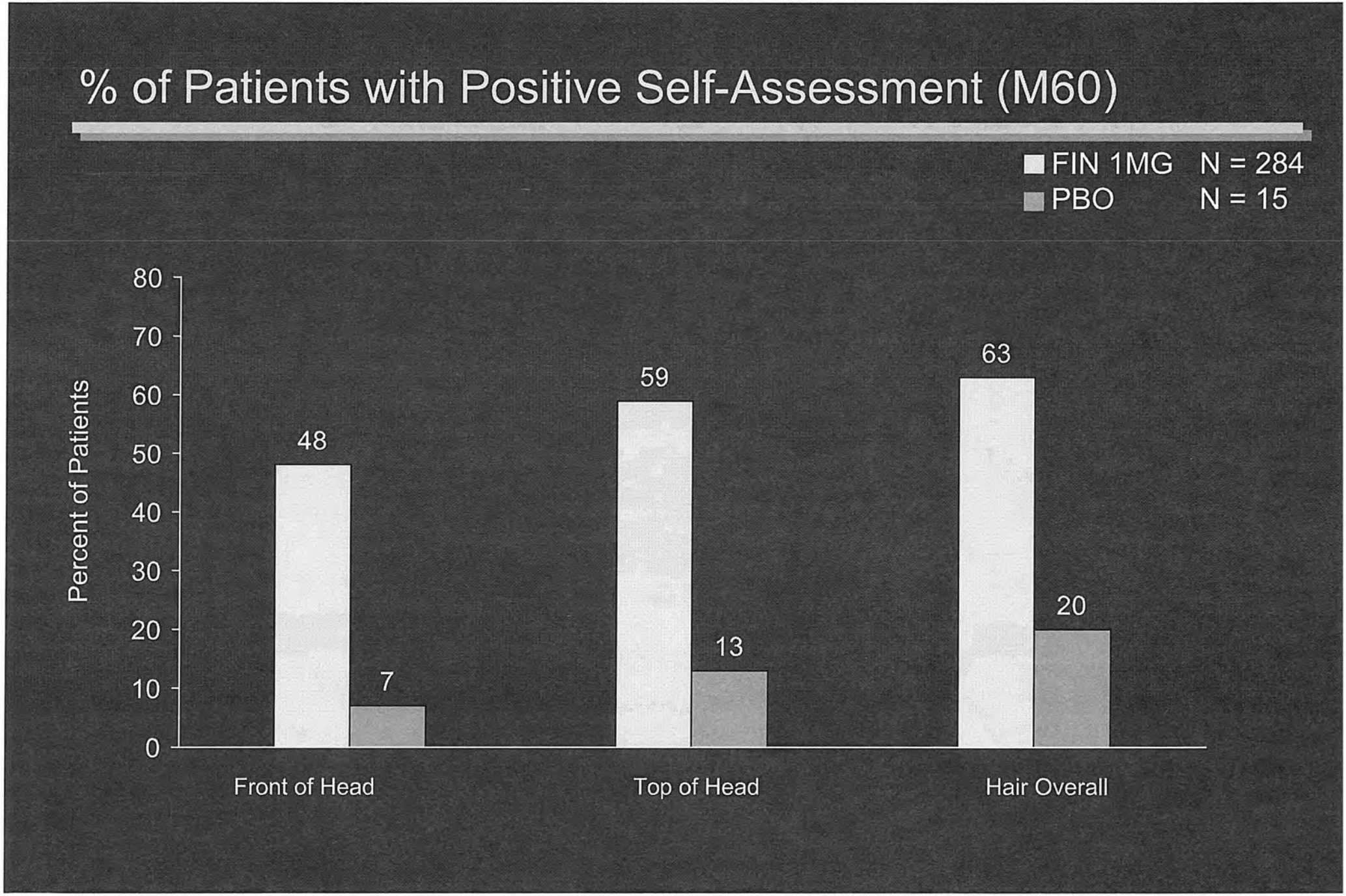

Investigator Assessment
FIN 1MG N = 271
PBO N = 13
Mean Change from Baseline ± SE
1.6
1.2
0.8
0.4
0.0
-0.4
-0.8
=1.3
=1.3
=1.9
=1.9
=2.0
Baseline
12
24
36
48
60
Month


Investigator Assessment (M60)
FIN 1MG N = 271
PBO N = 13
Percent of Patients
50
40
30
20
10
0
0
8
3
23
4
8
15
46
26
15
29
0
22
0
Greatly
Moderately
Slightly
No Change
Slightly
Moderately
Greatly
Decreased
Increased

Investigator Assessment (M24 vs. M60)

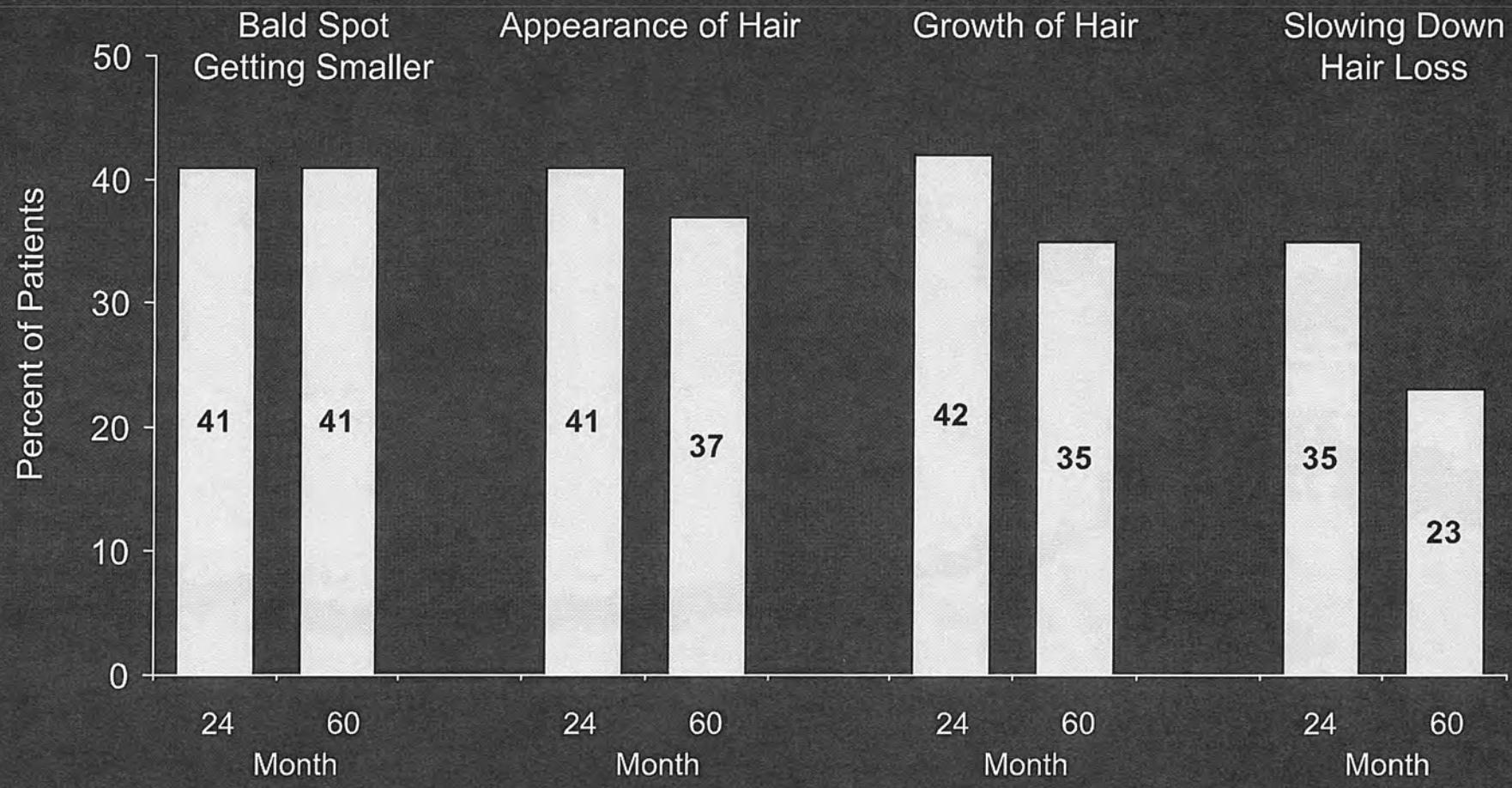



% of Patients with Positive Self-Assessment (M60)
FIN 1MG N = 284
PBO N = 15
Percent of Patients
90
80
70
60
50
40
30
20
10
0
61
20
77
40
75
40
90
67
Bald Spot Getting Smaller
Appearance of Hair
Growth of Hair
Slowing Down Hair Loss


% of Patients with Positive Self-Assessment (M60)
FIN 1MG N = 284
PBO N = 15
Percent of Patients
80
70
60
50
40
30
20
10
0
48
7
59
13
63
20
Front of Head
Top of Head
Hair Overall

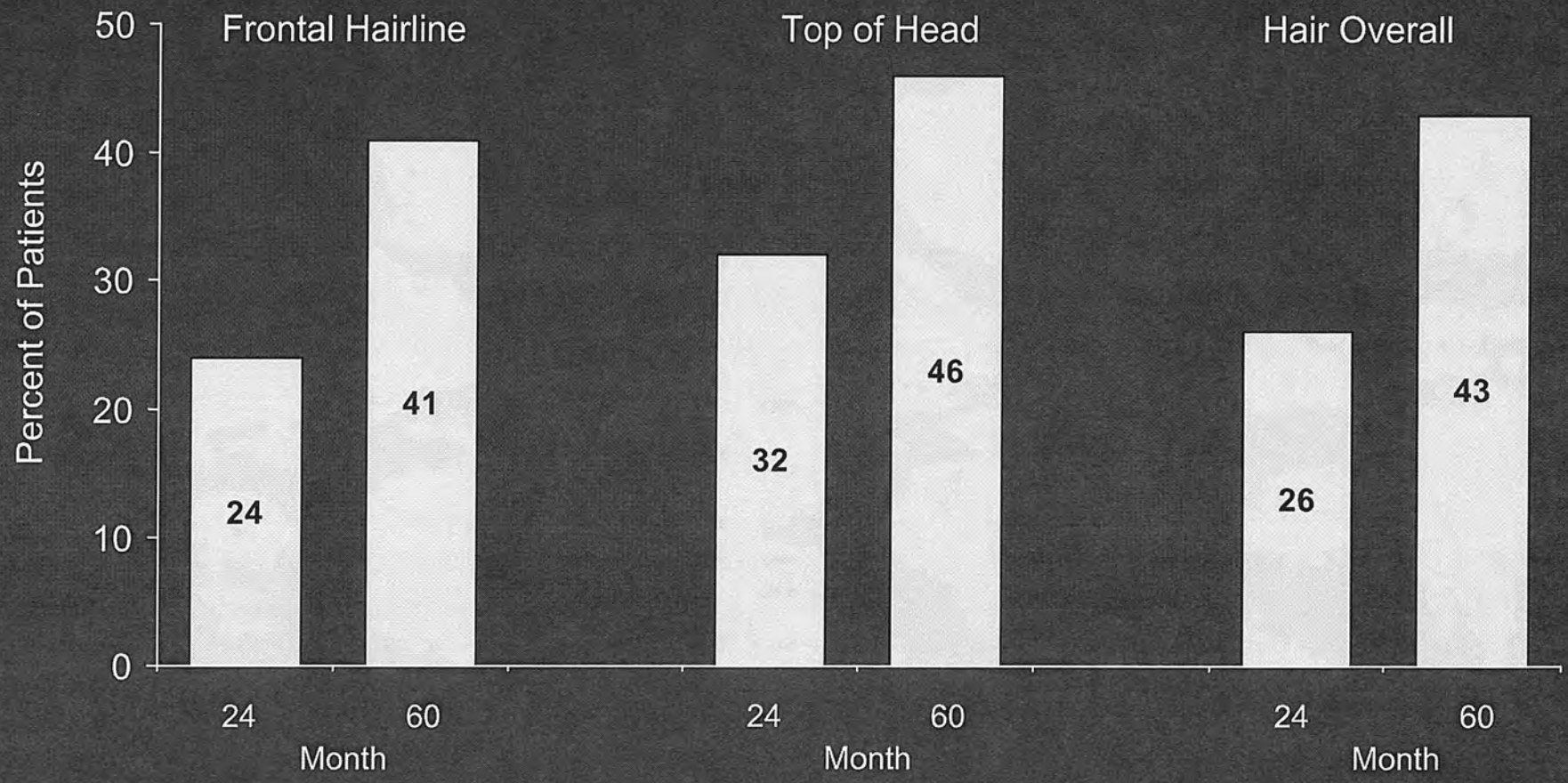
% of Patients with Positive Self-Assessment (M24 vs. M60)

Net Treatment Effect (Finasteride - Placebo)



% of Patients with Positive Self- Assessment (M24 vs. M60)

Net Treatment Effect (Finasteride - Placebo)



Drug-Related Sexual Adverse Experiences

Phase III Pivotal Studies - Year 5

	FIN 1MG (N = 323)	PBO (N = 23)
Number (%) of Patients with Any Drug-Related Sexual AE:	2 (0.6)	0
Libido Decreased	1 (0.3)	0
Erectile Dysfunction	1 (0.3)	0
Ejaculation Disorder	0	0
Decreased Ejaculate Volume	*0*	*0*
Any Sexually-Related AE Resulting in Discontinuation	0	0

Drug-Related Sexual Adverse Experiences

Phase III Pivotal Studies

	Year 1		Year 2		Year 3		Year 4		Year 5	
	FIN 1MG (N = 779)	PBO (N =774)	FIN 1MG (N = 547)	PBO (N = 60)	FIN 1MG (N = 447)	PBO (N = 46)	FIN 1MG (N = 379)	PBO (N = 33)	FIN 1MG (N = 323)	PBO (N = 23)
Number (%) of Patients with Any Drug-Related Sexual AE:	**34 (4.4)**	**17 (2.2)**	**9 (1.6)**	**1 (1.7)**	**4 (0.9)**	**0**	**2 (0.5)**	**0**	**2 (0.6)**	**0**
Libido Decreased	**15 (1.9)**	**10 (1.3)**	**7 (1.3)**	**1 (1.7)**	**1 (0.2)**	**0**	**1 (0.3)**	**0**	**1 (0.3)**	**0**
Ejaculation Disorder	**11 (1.4)**	**7 (0.1)**	**2 (0.4)**	**0**	**2 (0.4)**	**0**	**1 (0.3)**	**0**	**0**	**0**
Erectile Dysfunction	**11 (1.4)**	**5 (0.1)**	**4 (0.7)**	**0**	**1 (0.2)**	**0**	**1 (0.3)**	**0**	**1 (0.3)**	**0**
Any Sexually-Related AE Resulting in Discontinuation	**11 (1.4)**	**8 (1.0)**	**4 (0.7)**	**0**	**1 (0.2)**	**0**	**1 (0.3)**	**0**	**0**	**0**

PROPECIA: 5-Year Phase III Controlled Data

Conclusions

* Efficacy data support continued long-term benefit of PROPECIA
  - Progressive separation between groups by hair count
  - Some loss of treatment effect by global photography, but not observed in investigator or patient assessments
  - Patient satisfaction with appearance of hair overall increased with continued therapy
* Safety data support excellent long-term tolerability
* Data will be used 3T00 in US promotional material
  - Emphasize preventive benefit of PROPECIA
  - 5-yr Phase III CSR targeted for completion JAN01
* Regulatory filings with label updates are planned beginning 4Q00

PROPECIA

Regulatory Strategy for Filing 5-Year Data

Objectives of Filing the 5-Year Data in the EU

* Update SPC in countries where PROPECIA is currently approved
  - current SPC based on 24-month data
* Use long-term data in a repeat mutual recognition procedure to obtain approval in 6 outstanding countries

Need for Repeat Mutual Recognition

* At end of MR in 1998, marketing applications withdrawn in Austria, Belgium, Greece, Holland, Ireland, and Luxembourg
* Concerns primarily related to long-term safety and perceived negative risk/benefit ratio
* All 6 agencies also questioned efficacy including long term effect (beyond 2 years)

Impact of 5-Year Data on the SPC

Pharmacodynamic Properties Section

* SPC currently includes details of 12 and 24 month results for each of the 4 efficacy endpoints
* Type II Variation would propose a re-write of Pharmacodynamics Properties to include less detail and focus on treatment effect
  - qualitative description of long-term efficacy data with emphasis on stabilization of hair loss that occurs in the placebo group
  - shorter section more consistent with new SPC guidelines
* Agencies may insist on retaining current format with the addition of data from years 3-5

Possible Impact of 5-Year Data on the SPC

Indications Section

* Current indication includes a statement that PROPECIA *stabilizes* the process of androgenetic alopecia in men
* Decline from peak hair count between Months 24 and 60 may result in a change to the stabilization claim to suggest only a *slowing* or *delay* in the hair loss process

Proposed Regulatory Strategy in the EU

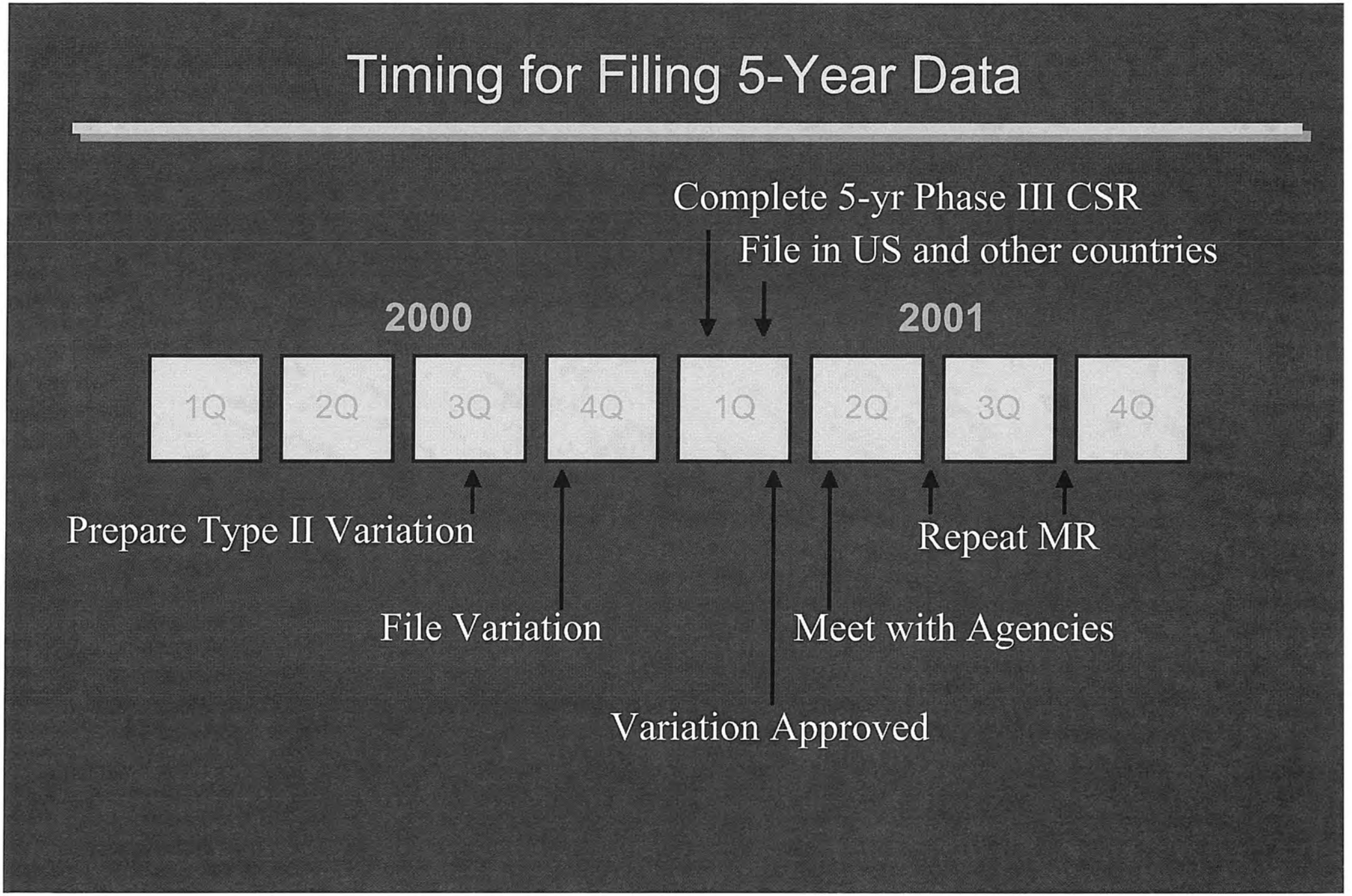
* 5-year data may be viewed differently by agencies who have approved PROPECIA than by those who have not
  - need to decrease risk of repeat MR by minimizing influence of outstanding countries
* File Type II Variation first to add 5-year data to SPC in countries where PROPECIA is approved
  - create consensus on the data and revised SPC

Proposed Regulatory Strategy in the EU

* Meet with agencies in outstanding countries to discuss new data and any remaining concerns
* Update marketing application to include 5-year data, post-marketing data, etc. to support approval in the outstanding countries
* File repeat MR procedure

Filing 5-Year Data in the Rest of the World

* Type II Variation will be filed in EU with 5-year data summarized in Expert Report and referenced by statistical memos
* CSR for Phase III Pivotal extension studies targeted for JAN01
* Plan to file label change supported by CSRs in US and other (non-EU) countries in 1Q01


Timing for Filing 5-Year Data
Complete 5-yr Phase III CSR
File in US and other countries
2000
2001
1Q
2Q
3Q
4Q
1Q
2Q
3Q
4Q
Prepare Type II Variation
File Variation
Variation Approved
Meet with Agencies
Repeat MR