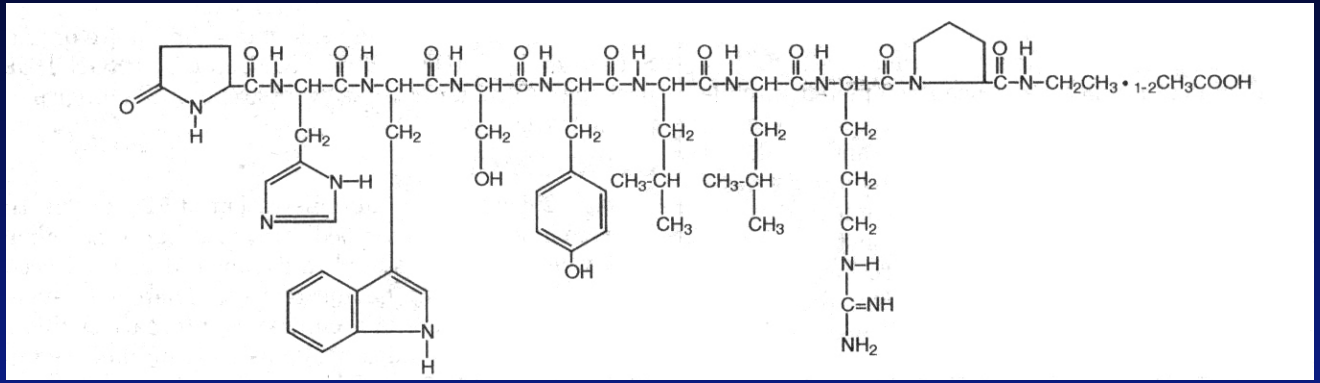
LEUPROLIDE



The ‘D’ is silent

David Redwine, M.D.
USA

"It is simply no longer possible to believe much of the clinical research that is published, ... I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine"

Marcia Angell
Former editor-in-chief NEJM

Studies of new drugs

Before mid-1980's:

Drug companies gave unrestricted money to medical schools.

designed and conducted studies
controlled the data
interpreted the data
published the data

After the mid-1980's:

drug companies control all steps

Lupron

FDA-approved in 1990 for treatment of endometriosis

Clinical studies began in mid -1980's.

Studies were devised, developed, and conducted by TAP (Takeda/Abbott Pharmaceuticals)

Results were presented to the FDA, which approved Lupron; journal publications followed

Lupron

Do Marcia Angell's comments about disbelieving clinical research apply to Lupron?

Should we believe what has been published about Lupron?

Important question!

Millions of women have endometriosis

Lupron is widely prescribed worldwide

Similar drugs are on the market in different countries

Is Lupron safe and effective?

Lupron

Proprietary studies by TAP submitted to FDA:

M84-042
M86-031
M86-039
M86-050
M90-471
M91-601
M92-878
M96-506
M97-777

All these studies were placed under a federal court seal in 2011 at the request of Abbott (which acquired sole rights to Lupron in 2008)

Lupron

Why doesn't Abbott want anyone to see these studies?

M84-042
M86-031
M86-039
M86-050
M90-471
M91-601
M92-878
M96-506
M97-777

Proprietary financial protection?

Lupron will be off patent soon

Everyone knows the chemical formula

NO

Copy-cat medicines are marketed

Lupron

Why doesn't Abbott want anyone to see these studies?

Protection of intellectual property?

- Lupron will be off patent soon
- Everyone knows the chemical formula
- Copy-cat medicines are marketed

NO

Lupron

Why doesn't Abbott want anyone to see these studies?

Let's examine some of the studies and see why

How did I get the studies?

Klein vs Abbott, United States District Court Case 2:08-CV-00681

Lupron

Klein vs Abbott, United States District Court Case 2:08-CV-00681

Abbott offered all studies as exhibits

The study information included raw data, summary conclusions

Abbott moved that all studies except one be excluded from testimony

The judge agreed

All studies were stacked on the witness stand throughout the trial

Witnesses were not allowed to talk about them

Lupron

Methodology for each study review

Study #

- Estrogen levels
- Bone mineral density
- Adverse events
- Efficacy
- Discussion

The study as represented in the medical literature

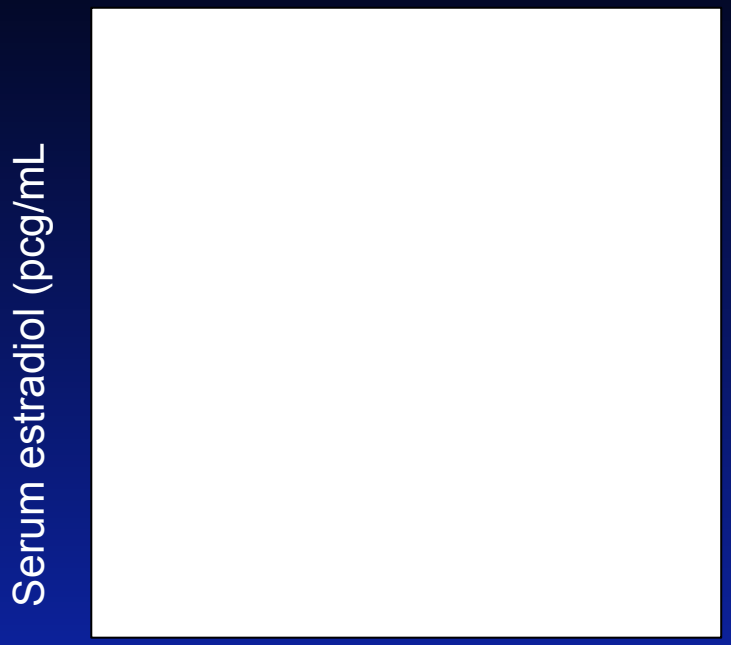
Lupron

Raw data were reviewed to see if conclusions were supported by the data.

M84-042

Phase II study
- Lupron sub Q daily x 7 days
- Lupron nasal spray x 26 weeks
- One year follow-up
- Comparison drug: danazol

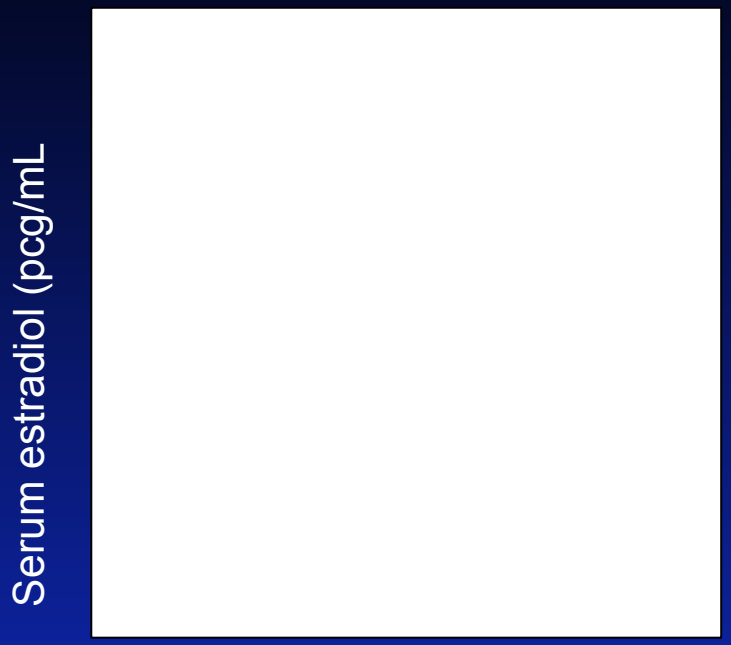
M84-042 (estrogen)



Estradiol levels – pre-Rx and one year follow-up

But: patient 115 had a protocol violation: 15 month E2 level of 253 was used instead of 12 month E2 level of 66.8

M84-042 (estrogen)



24% increase
in mean E2 level
at 1 year after Rx!

Estradiol levels – pre-Rx and one year follow-up

After correction of protocol violation

M84-042 (estrogen)

Estradiol levels – baseline vs 1 year

5/8 (63%) did not regain baseline
4/8 (50%) estradiol levels were below 100
1/8 (13%) had menopausal E2 level

Several 1 – year E2 levels were taken; results are not due to 'outliers'

Conclusion from the raw data: Lupron suppresses ovarian function long term in most patients. ? permanent in some?

TAP's conclusion: Hormonal profiles during the follow-up period were similar to baseline.

Intentionally misleading and based on protocol violation

M84-042 (estrogen)

Estradiol levels – baseline vs 1 year

Effect of small numbers: 8 patients

Too few to make any conclusion?

M84-042 (BMD)

BMD measured in spine by dual photon method at baseline before treatment and within 30 days of end of therapy. N = 16

There were several protocol violations related to timing of BMD studies.

% loss of spine BMD:

Including 5 patients with protocol violations: -2.3%

Excluding 5 patients per protocol: -2.6%

M84-042 (BMD)

Conclusion from RAW DATA:

mean BMD loss ranges from - 2.6% to – 7.3%, with some patients losing over 18%.

TAP's conclusion: "Leuprolide acetate patients had a 2.3% mean decrease in BMD during the 26 week study"

Inconsistent protocol application can improve results.

Not mentioning bad results makes them go away.

M84-042 (BMD)

FDA labeling in 1990: (We observed) “a small loss in bone density over the course of treatment, some of which may not be reversible. During one six-month treatment period, this bone loss should not be important.”

The possibility of irreversible bone loss is unimportant?

Lesson: Gratuitous, unsupportable trivialization or non-mention of unfavorable results is reassuring.

M84-042 (BMD)

BMD measured in spine by CT at baseline before treatment and within 30 days of end of therapy.
N = 3

% BMD loss: 9.7%

M84-042 (BMD)

Neither the real 2.6% loss nor the 9.7% loss was mentioned in the summary.

M84-042 (in literature)

Gynecology-endocrinology

FERTILITY AND STERILITY
Vol. 51, No. 3, March 1989

Printed in U.S.A.

A randomized, prospective comparison of endocrine changes induced with intranasal leuprolide or danazol for treatment of endometriosis*†

Ian S. Tummon, M.D.‡
Margaret E. Pepping, M.S., R.N.
Zvi Binor, M.D.
Ewa Radwanska, M.D.
W. Paul Dmowski, M.D., Ph.D.

No mention of real BMD loss.
No mention of 12 month post treatment follow-up results!!
No further studies on long-term ovarian function
Paper sponsored by TAP

M84-042 (estrogen)

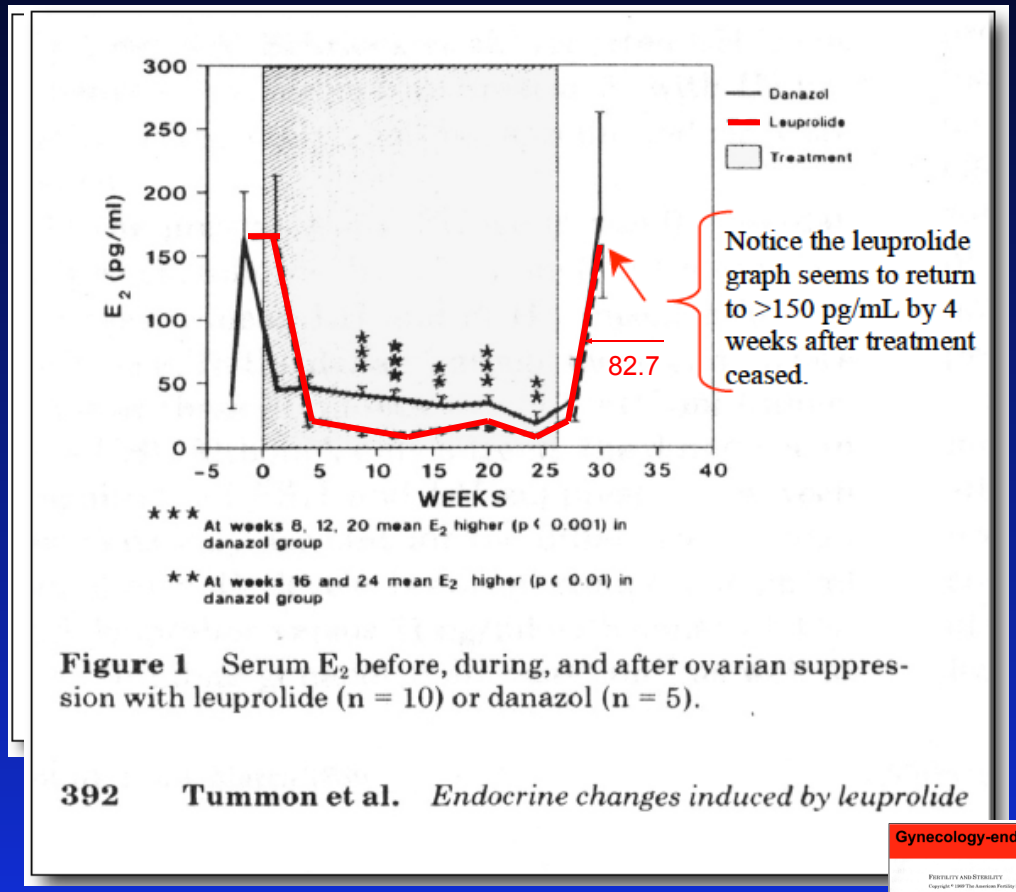
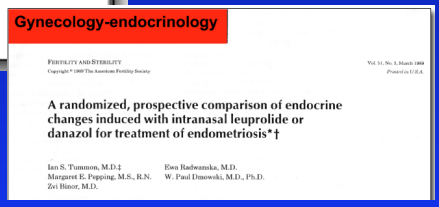


Figure 1 Serum E_2 before, during, and after ovarian suppression with leuprolide (n = 10) or danazol (n = 5).

Post treatment E2 artificially increased by almost 100% !!

Same graph from *Fertility and Sterility*



M84-042 (progesterone)

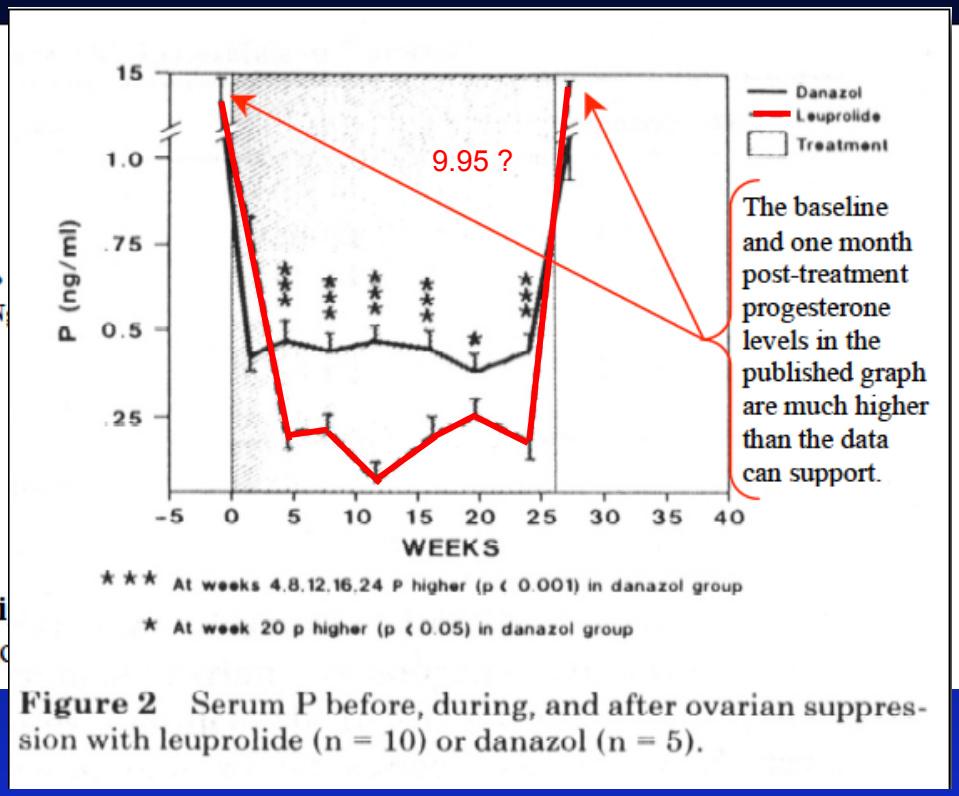
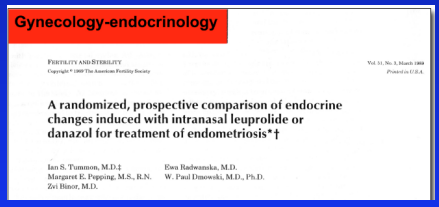


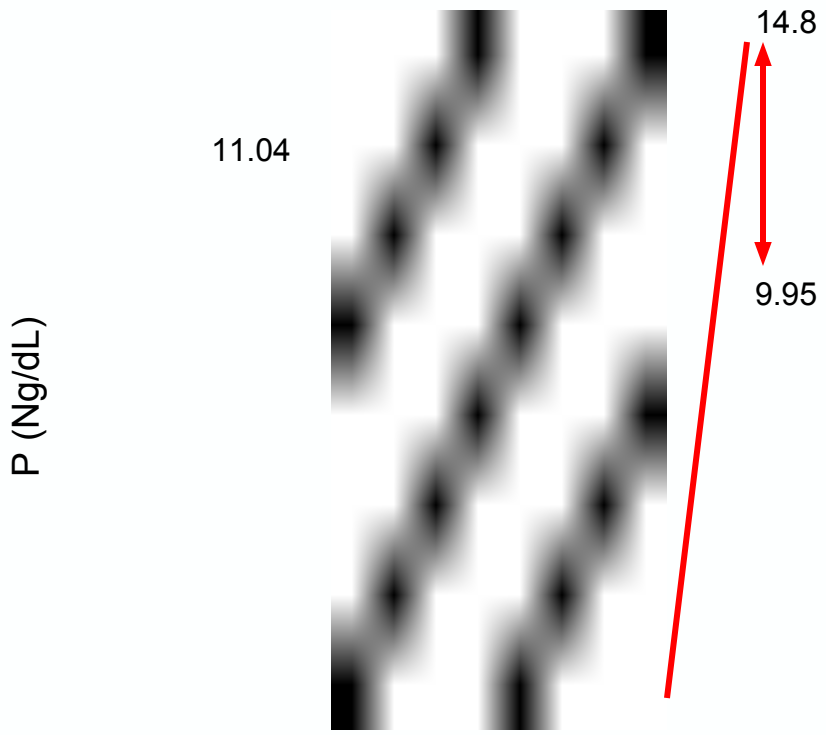
Figure 2 Serum P before, during, and after ovarian suppression with leuprolide (n = 10) or danazol (n = 5).

Lesson: if a graph is unfavorable, just alter it with the help of an axis break that prevents accurate graphing of post-Rx value

Same graph from *Fertility and Sterility*



M84-042 (progesterone)



From the Fertility Study

M84-042 (Efficacy)

Treatment failure (dropouts):

6.9%

M86-031 (BMD)

Phase 3 RCT (38 Lupron v 24 placebo)
Lupron 3.75 mg IM q 4 wks x 6 months

Patients with known causes of bone loss were excluded
BMD checked in multiple ways

2 Lupron patients were included against protocol
- one did not have endometriosis
- one did not have sufficiently severe symptoms

M86-031 (BMD)

Bone loss averages in Lupron patients:

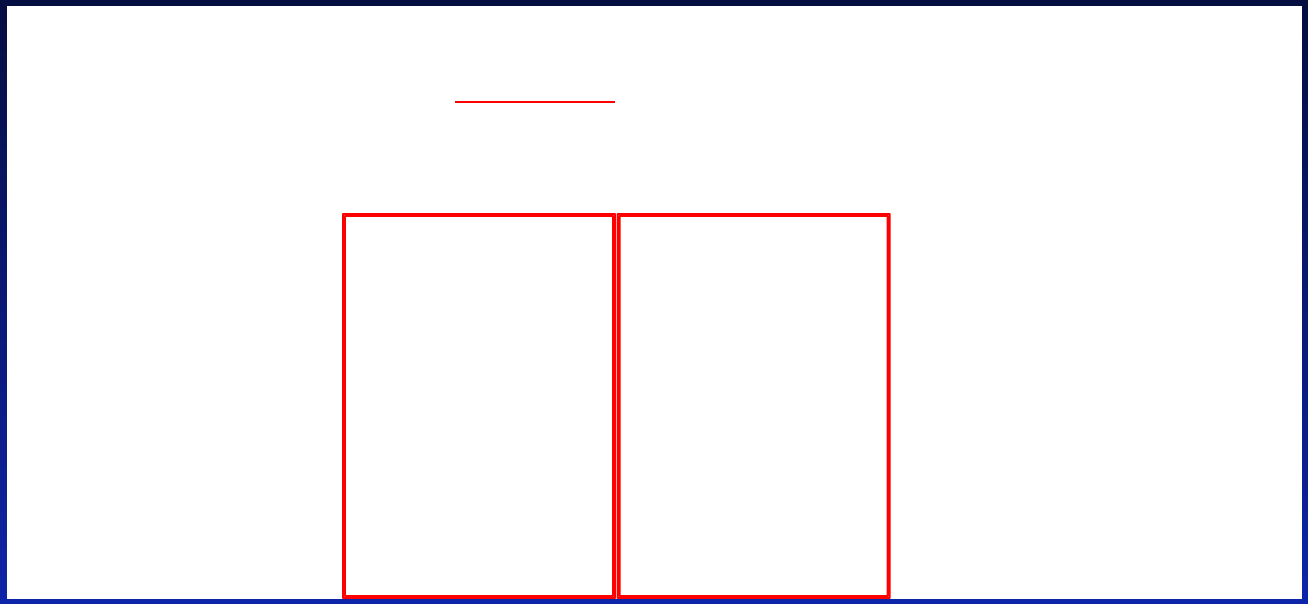
- 4.0% from spine by DP
- 7.0% from wrist by CT
- 10.5% from wrist by single photon
- 11.8 % from spine by CT

Conclusion: Lupron Depot was shown to be safe and effective in inducing hormonal and menstrual suppression in patients with endometriosis. This resulted in alleviation of pain and other symptoms.

Conclusion: Bone loss up to 12% is safe

M86-031 (efficacy)

Pain persistence in *successful completers*:



Dysmenorrhea (a uterine symptom) is the symptom responding best to Lupron)

Most patients do not achieve relief of endometriosis signs or symptoms

M86-031 (efficacy)

Pain persistence, corrected for placebo effect and dropouts:

Symptom	Baseline Corrected for Dropouts		Final visit at 24 weeks Corrected for dropouts		Rate corrected for Placebo effect
Dysmenorrhea	29/31	(93.5%)	7%	3/31 (9.7%)	14.7%
Pelvic pain	28/30	(93.3%)	57%	18/30 (60.0%)	70.0%
Dyspareunia	16/18	(88.9%)	59%	11/18 (61.1%)	69.1%
Pelvic tenderness	28/31	(90.3%)	61%	18/31 (58.1%)	72.1%

Conclusion: Lupron Depot was shown to be safe and effective in inducing hormonal and menstrual suppression in patients with endometriosis. This resulted in alleviation of pain and other symptoms. **In a minority of patients**

M86-031 (efficacy)

28/28 (100%) of patients on Lupron required some type of pain medicine

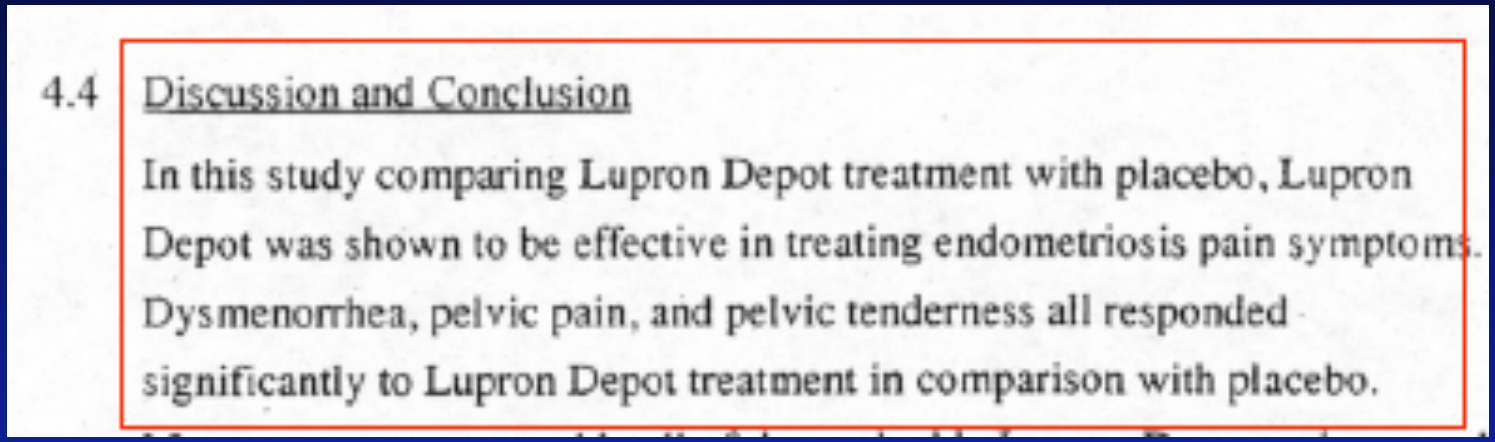
15/28 (53.6%) of evaluable patients required narcotic pain medicine during treatment, two of these during initial symptom flare

13/28 (46.4%) used narcotic pain medicine after the initial symptom flare.

Conclusion: Lupron is not very effective if most patients still require narcotics during Rx

M86-031 (efficacy)

TAP's conclusion regarding efficacy:



4.4 Discussion and Conclusion

In this study comparing Lupron Depot treatment with placebo, Lupron Depot was shown to be effective in treating endometriosis pain symptoms. Dysmenorrhea, pelvic pain, and pelvic tenderness all responded significantly to Lupron Depot treatment in comparison with placebo.

Lessons:

call failure a success

replace quantitative deficiencies with more favorable qualitative descriptors

M86-031 as reflected in the literature

FERTILITY AND STERILITY
Vol. 54, No. 3, September 1990

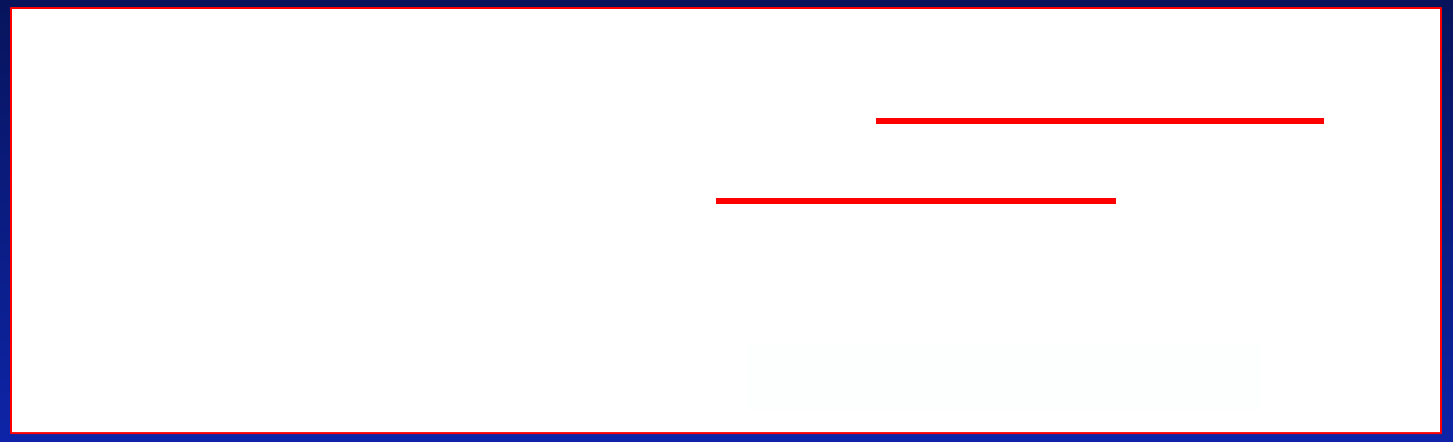
Printed on acid-free paper in U.S.A.

Lupron* depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo-controlled, double-blind study†

Alexander M. Dlugi, M.D.‡
James D. Miller, M.D.§
Judith Knittle*
Lupron Study Group‖

Henry Ford Medical Center, Grosse Pointe Farms, Michigan; University of Washington, Seattle, Washington and TAP Pharmaceuticals, North Chicago, Illinois

M86-031 as reflected in the literature



Two Lupron patients were to have all data excluded

M86-031 as reflected in the literature

Patients 412 and 421 were included in BMD calculations

M86-031 as reflected in the literature

data could not be adequately evaluated. Nevertheless, 15 LA patients who had spinal bone mineral density assessed by dual photon absorptiometry demonstrated a mean decrease of 3.6% ($P = 0.001$)

Fertility and Sterility

When the patients 412 and 421 are properly excluded, N = 13 and loss of BMD becomes 4%, not 3.6%.

11% improvement in BMD by this protocol violation

M86-031 as *unreflected* in the literature

After 6 months of treatment: 75% still have pain (corrected for dropouts and placebo effect).

During treatment, over 50% required narcotics for pain relief.

Bone loss between 4% and 11.8% over 6 month treatment period.

Protocol violations (inclusion of patients who were to be excluded) made Lupron look better.

M86-031 as reflected in the literature

Conclusion:

Lupron depot was shown to be safe and effective in inducing hormonal and menstrual suppression in patients with endometriosis. This resulted in significant alleviation of pain and other symptoms. Many patients benefited from LA treatment long after the time of drug exposure.

Was this long-term benefit related to ovarian dysfunction?

M86-039

Phase III double blind RCT comparing Lupron (N=134) v Danazol (N=136) x 24 weeks

Scientifically untrue

M86-039 (BMD)

Spine BMD checked by quantitative CT at baseline and after 6 months Rx

Average BMD loss was - 7%

TABLE 26

PERCENT CHANGES IN BONE MINERAL DENSITY AND BONE MIN

SITE	TREATMENT GROUP	PATIENT	BONE MINERAL DENSITY BASELINE	BONE MINERAL DENSITY FINAL	BONE MINERAL DENSITY CHANGE	PERCENT CHANGE
SPINE-CT SCAN (MG/CM3) @						
	LUPRON DEPOT	577 (DA)	158.4	243.5	85.1	53.7
		578 (DA)	241.9	205.5	-36.4	-15.0
		637 (DA)	160.6	141.6	-19.0	-11.8
		640 (DA)	158.1	133.8	-24.3	-15.4
		641 (DA)	197.2	168.2	-29.0	-14.7
		543 (GA)	205.0	186.0	-19.0	-9.3
		507 (W)	158.8	114.6	-44.2	-27.8
		508 (W)	138.7	116.5	-22.2	-16.0

BUT:

+53.7%!!

This patient data was to be discarded.

Corrected BMD loss rises to - 15.7%

M86-039 (BMD)

Hip BMD checked by DPA at baseline and after 6 months Rx

"Average BMD loss was – 2.7%"

BUT:

+40.8%!!

Corrected BMD was – 3.8% not – 2.7%

This patient data was not discarded.

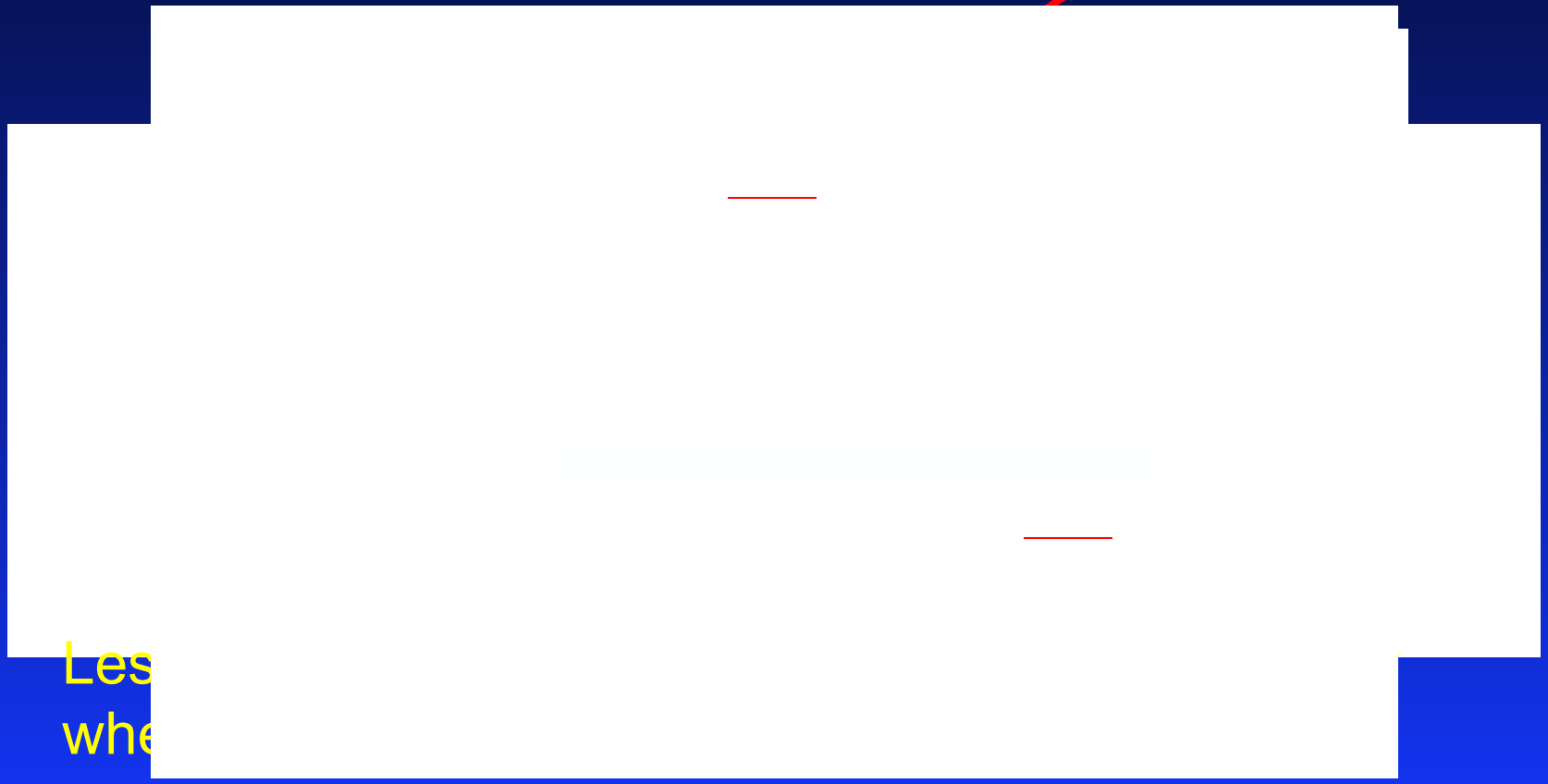
41% change in favor of Lupron!

M86-039 (BMD)

From raw data:

Spine BMD loss (corrected): - 15.7%

Hip BMD loss (corrected): - 3.8%



Les
whe

M86-039 (response of rAFS score at end of treatment)

Possible number of combination of points

4
4
4
4
4
4
3

4
4
4
4
4
4
4
4

$4^{14} \times 3 = 805{,}310{,}000$ possible combinations

M86-039 (response of rAFS score at end of treatment)

Assignment of points

7
12
7
40
7
40

113 possible endometriosis points

44
7
28
7
28
7
28
7

184 possible adhesion points

297

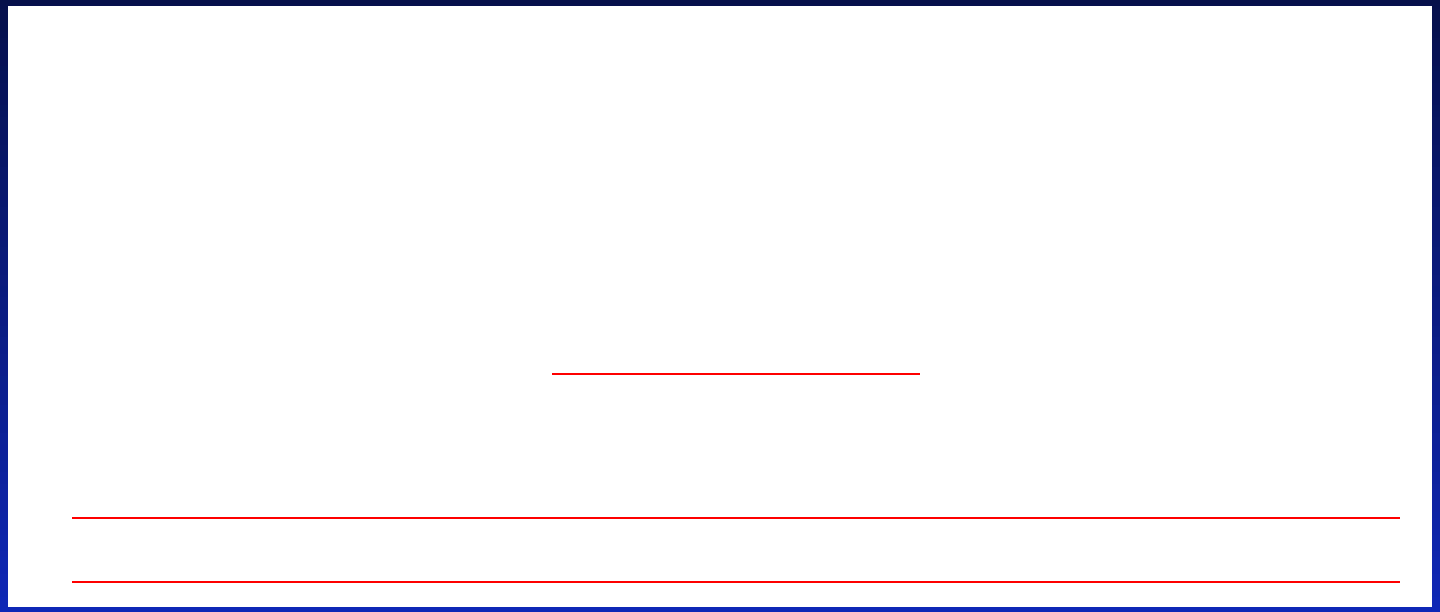
rAFS classification of endometriosis is an adhesion classification

M86-039 (response of rAFS score at end of treatment)

Evers JLH,
The second-look laparoscopy for evaluation of the result of medical treatment of endometriosis should not be performed during ovarian suppression.
Fertil Steril 1987, 47:502

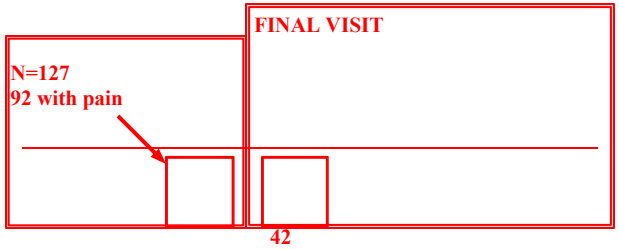
Visual response to Lupron: not important

M86-039 (response of pain)



During Lupron therapy, there is no reduction in requirement of pain medicine!!!

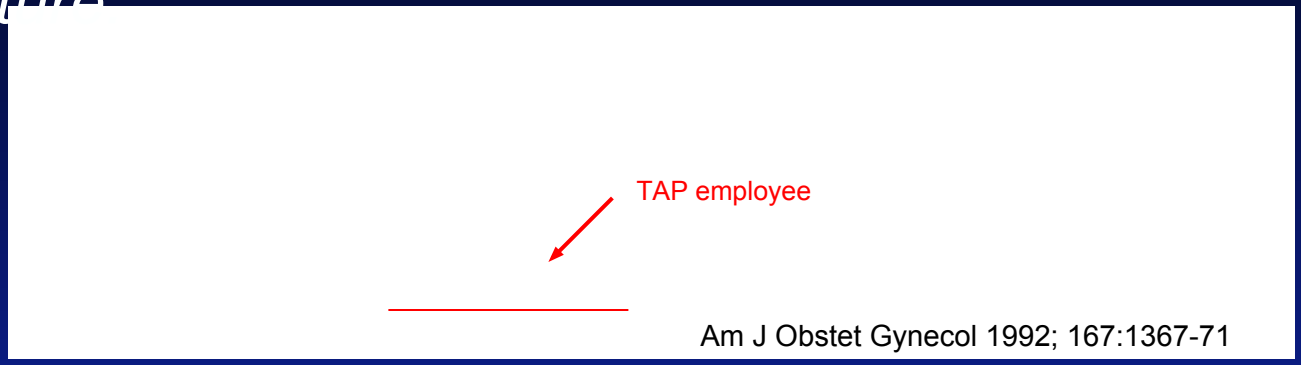
M86-039 (response of pain)



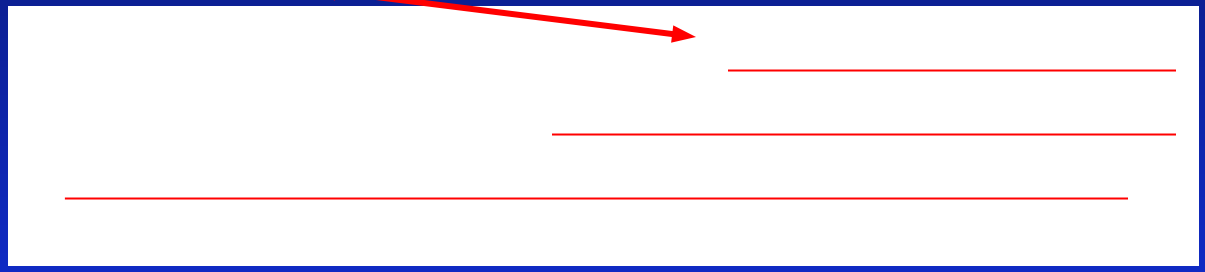
42/92 (46%) had complete resolution of pelvic pain at final visit

M86-039 (response of pain)

From the literature:

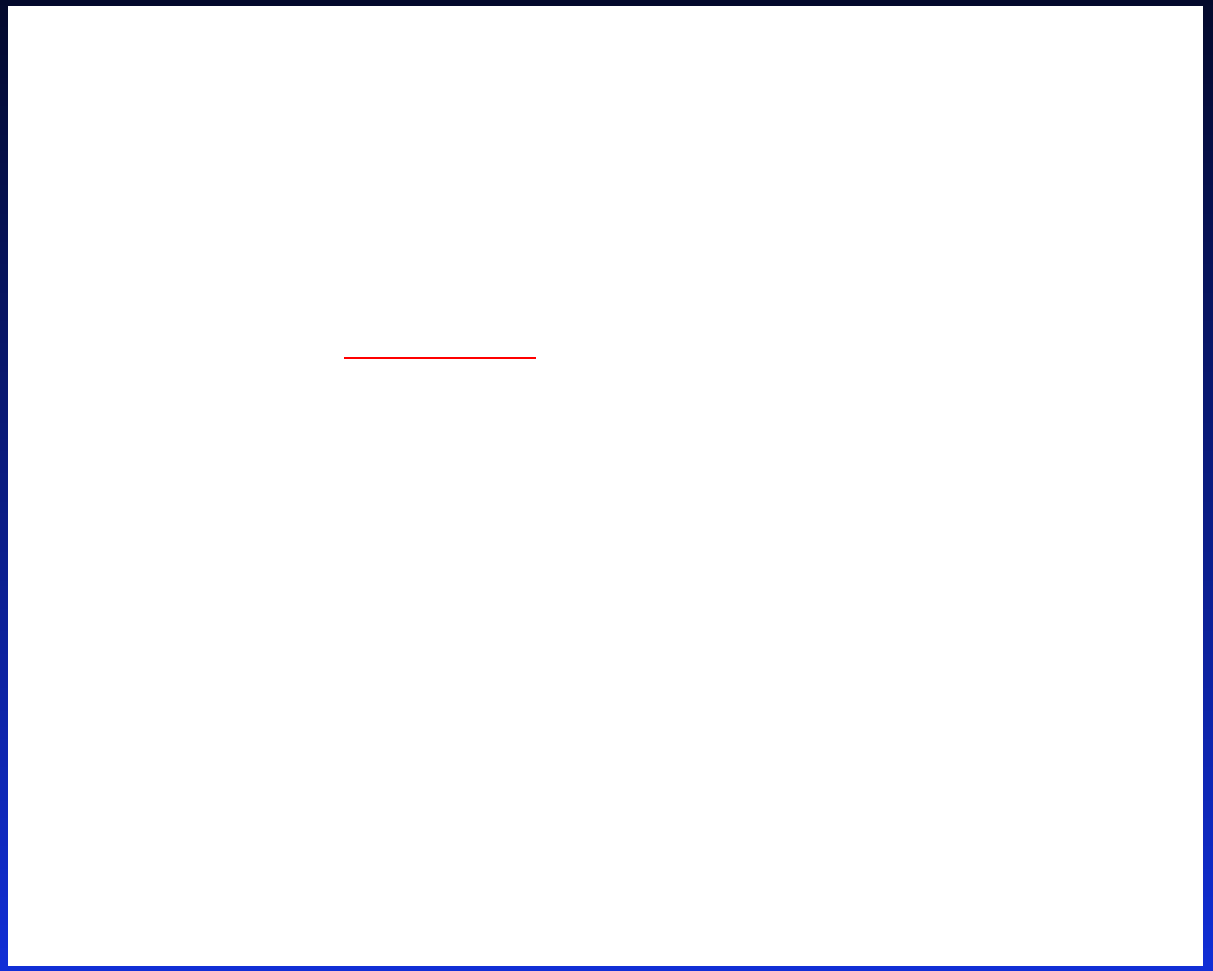


Just seen: 46% had complete relief of pelvic pain



Evidence-based medicine: 55% is higher than the 46% shown by the raw data.

M86-039 as reflected in the literature



Protocol violations, artificially high BMD values not mentioned

M90-471

Lupron 3.75 mg x 6 months (n=37)

Comparison drug: Synarel

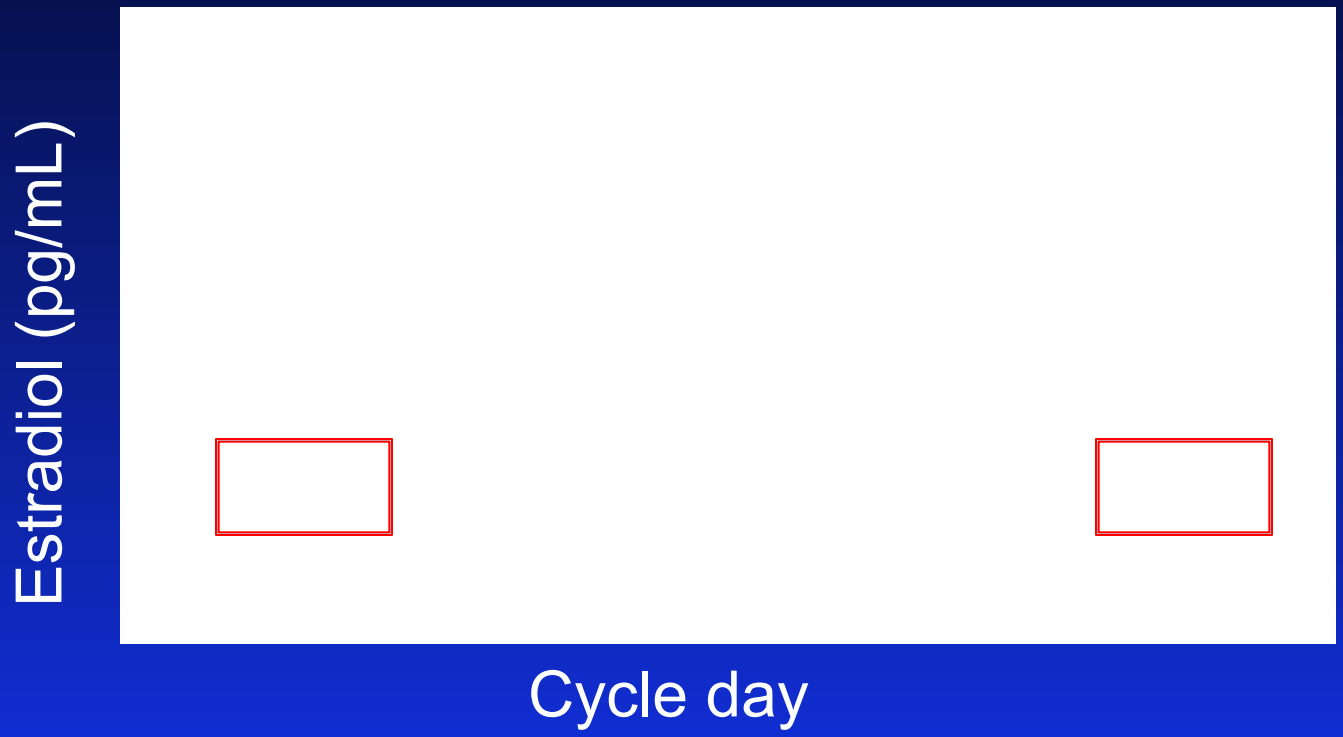
‘Safety’ measure: vaginal bleeding after cessation of Rx

Baseline estradiol before Lupron Rx: 61 pg/mL

61 pg/mL ??

M90-471 (estrogen)

Baseline estradiol before Rx: 61 pg/mL

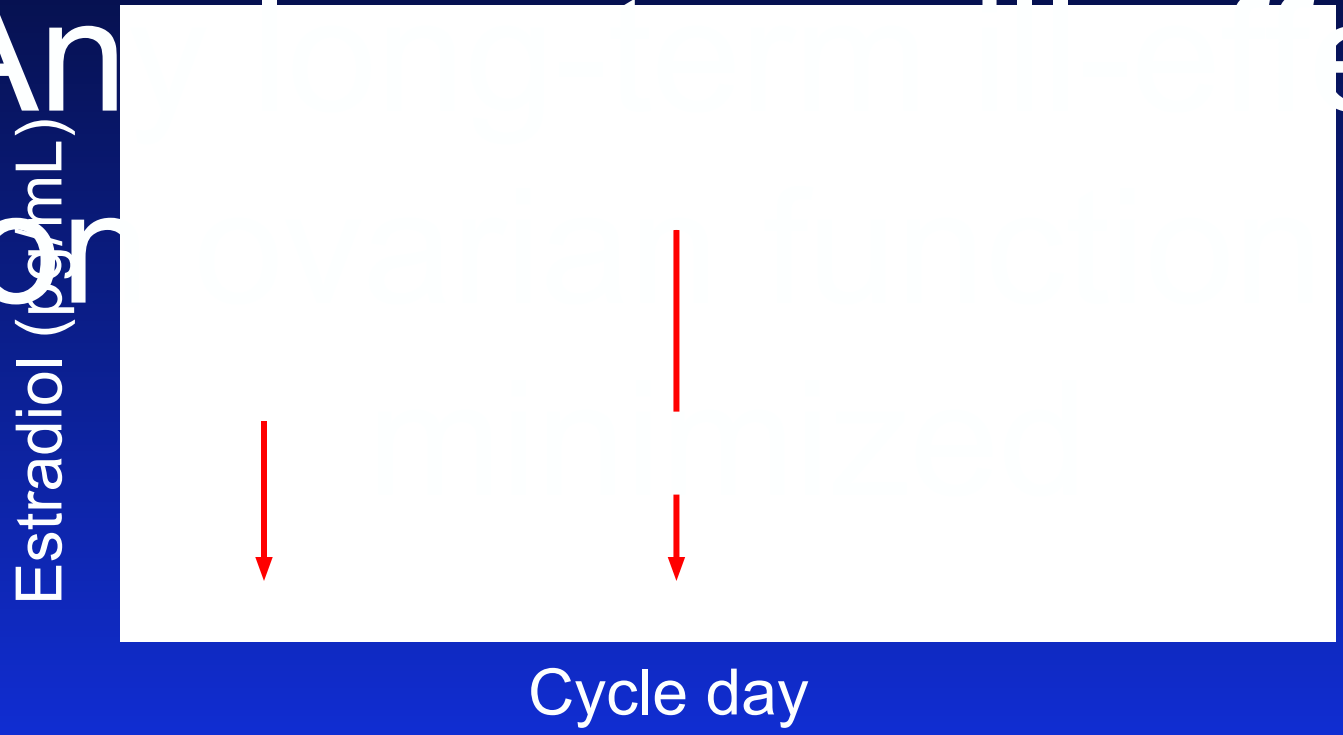


WHY?

M90-471 (estrogen)

Baseline estradiol before Rx: 61 pg/mL

An [illegible] effect
On [illegible] is



WHY? Because the maximum E2 drop is 61

M90-471 (‘safety’)

Any vaginal bleeding after cessation of Lupron	=	Recovery of normal ovarian function

HOW VALID IS THIS AS A ‘SAFETY’ TEST?

M90-471 ('safety')

Any vaginal bleeding after cessation of Lupron = Recovery of normal ovarian function

Hormonal function after vaginal bleeding:

In other words, there appeared to be evidence of recovery of hormonal function in women with evidence of recovery of hormonal function

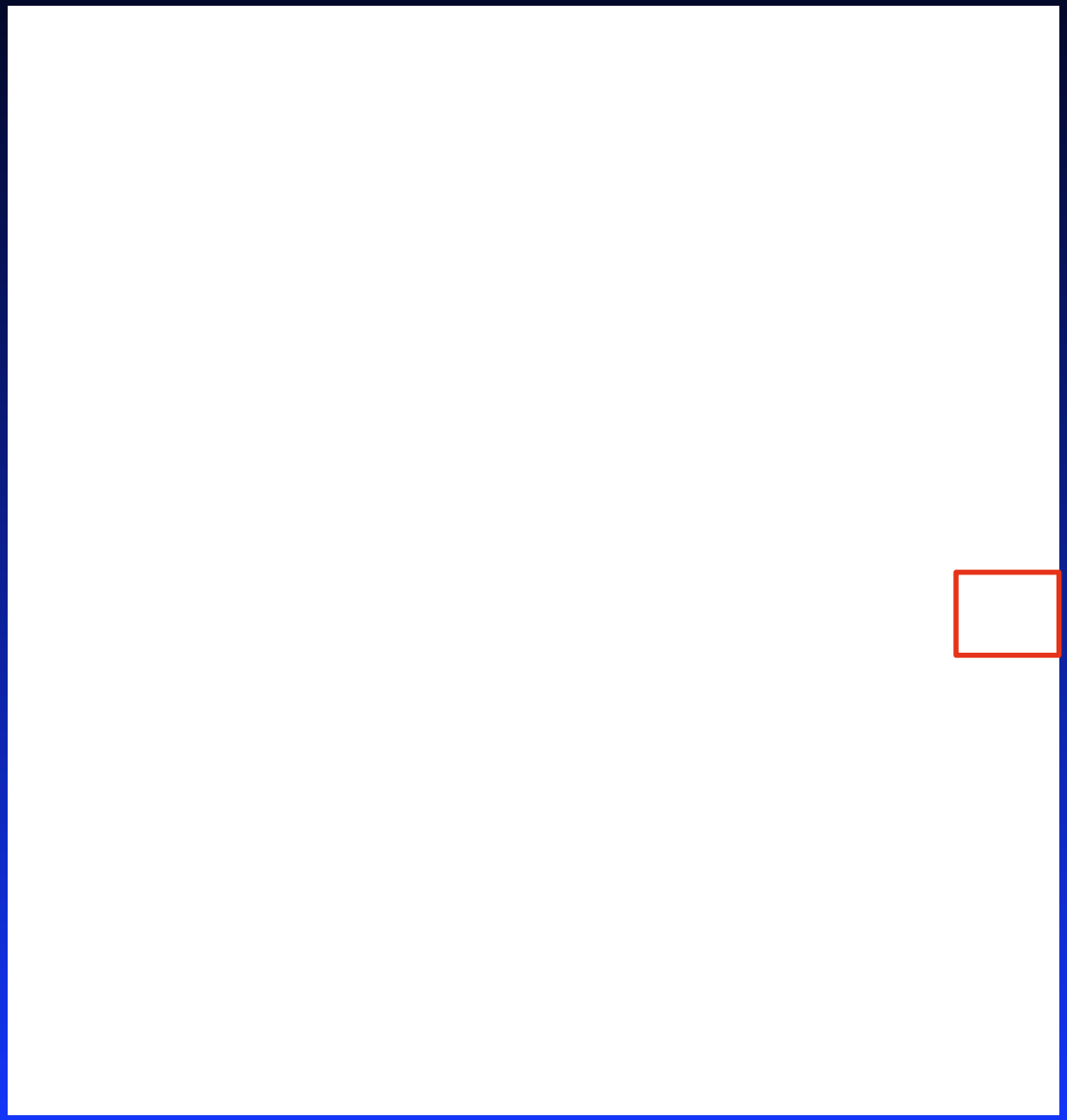
This is a meaningless circularity!!

M90-471 (estrogen)

With first vaginal bleeding, estradiol had fallen 4.4% from the already low baseline (n = 34)

3/37 patients (8%) did not have return of vaginal bleeding. Lupron was not ‘safe’ for them.

M90-471 (BMD)

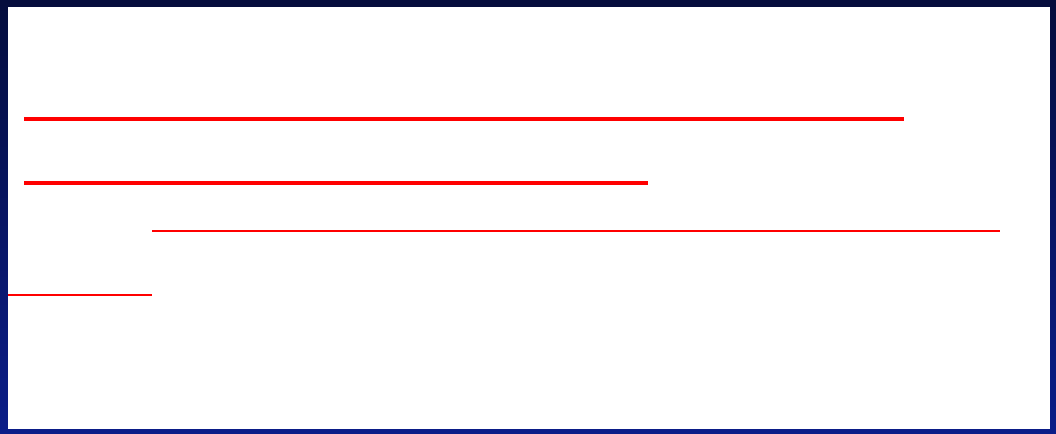


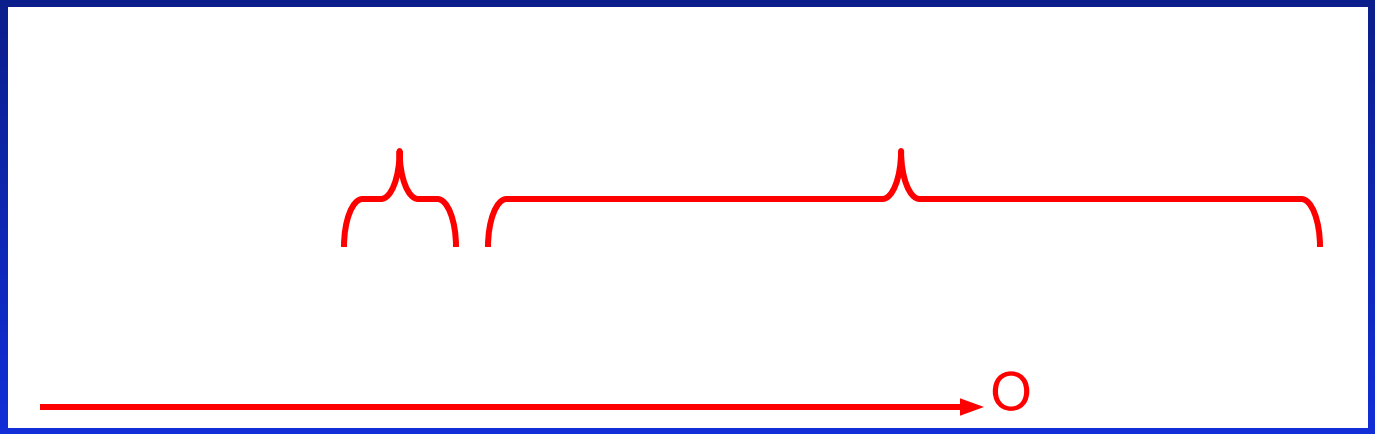
Raw data:
9 patients in bold were to be excluded for technical reasons.

10.5% loss of BMD

M90-471 (BMD)

Patient # 1148 was excluded:





Patients were screened pre-Rx for thyroid disease
#1148 could have been included up to 6 months after Rx

M90-471 (BMD)

Outcome from raw data table is totally confusing because N's don't match:

29	-3.5
20	-3.0
4	-1.3
20	-2.6

With inclusion of #1148 and other non-excluded patients from raw data table

Lesson: don't let reality get in the way of success

M90-471 (Adverse events)

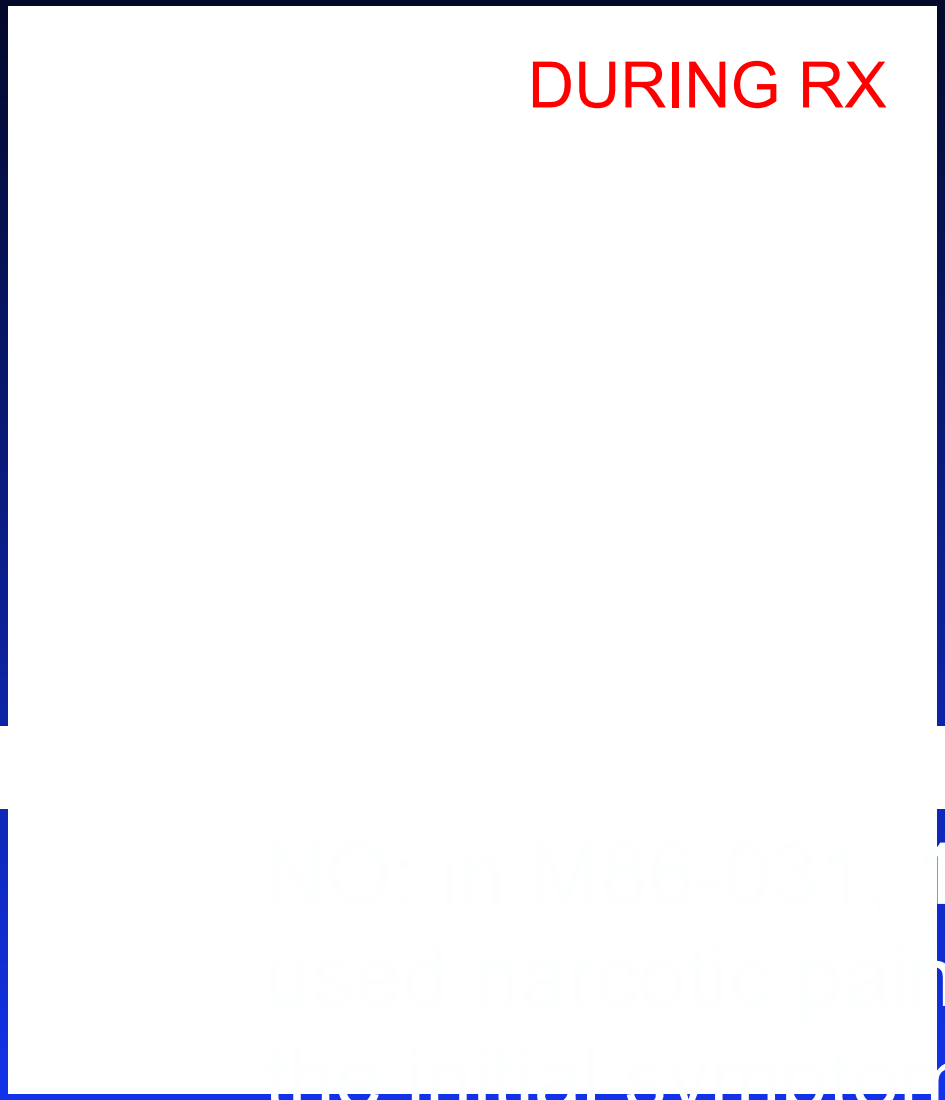
Prevalence (P) of adverse events at 12 months after Lupron was stopped:

N = 14 Lupron pts

Adverse event		N	P%
Headache	6	43	
Back pain	3	21	
Dyspepsia	3	21	
Anxiety	3	21	
Pelvic Pain	2	14	
Breast pain	2	14	

The drug sponsor declared these effects were not due to the drug but had no evidence to support this conclusion

M90-471 (Efficacy for pain)



54.5% of patients required narcotics during Lupron Rx
? Due to flare?

13/28 (46.4%) medicine after flare

M90-471 (Efficacy for pain)

50% of patients required narcotics after Lupron Rx

M90-471 (Efficacy for pain)

21% of women with non-menstrual pelvic pain had no improvement (page xi)

“The majority of patients reported return of symptoms (return to baseline) at the 6 months follow-up or later.”

Unimpressive results – why bother?

M91-601

Multicenter double-blind RCT

Lupron (n=101) vs lo-Ovral bcp

6 months Rx

12 month post-Rx observation

M91-601 Adverse events after Rx

N = 42 Lupron pts Prevalence at months 9 – 12 after Lupron therapy stopped

Adverse event	N	P%
Headache	19	45
Migraine	4	10
Back pain	4	10
FIu Syndrome	4	10
Asthenia	4	10
Pain	4	10
Nausea	3	10
Breast pain	3	10
Vasodilatation	1	2

M91-601 Efficacy

Treatment discontinuation – possible categories

Medical Rx of endometriosis
Surgical Rx of endometriosis
Worsening of disease
Adverse event
Patient request
Pregnancy

M91-601 Efficacy

Example:

If ‘Patient request’ is taken as the main reason for terminating follow-up, it sounds better.

M91-601 Efficacy

Dropout reasons in the one-year no treatment follow-up period: (Lupron n = 46)

Possible reasons (8/46 - 17% - had more than one reason)

- Patient request
- Patient request
- Worsening of disease
- Surgical treatment for endometriosis
- Adverse event
- Patient request
- Pregnancy
- Lost to follow-up

Of 10, 5 had a worse reason

‘Patient request’ sounds better than more medical or surgical Rx

M91-601 Efficacy

Dropouts in the one-year no treatment follow-up period:
(Lupron n = 46)

M91-601 Efficacy

Dropouts in the one-year no treatment follow-up period:
(Lupron n = 46)

Reason for premature termination of follow-up	Lupron Depot	
	Original	Revised
Medical Treatment for endometriosis	17 (36.9%)	[illegible]
Patient request	10 (21.7%)	[illegible]
Pregnancy	7 (15.2%)	7 (15[illegible]
Worsening of disease	4 (8.7%)	[illegible]
Lost to Follow-up	4 (8.7%)	[illegible]
Adverse Event	3 (6.5%)	3 ([illegible]%)
Surgical Treatment for endometriosis	1 (2.2%)	3 (6.5%)

M91-601 Efficacy

To make Lupron look even better compared to lo-Ovral:

Do not allow tabulation of ‘patient request’ in a summary table when another, worse reason exists that can make lo-Ovral look bad

This was not an innocent ‘error’

M92-878

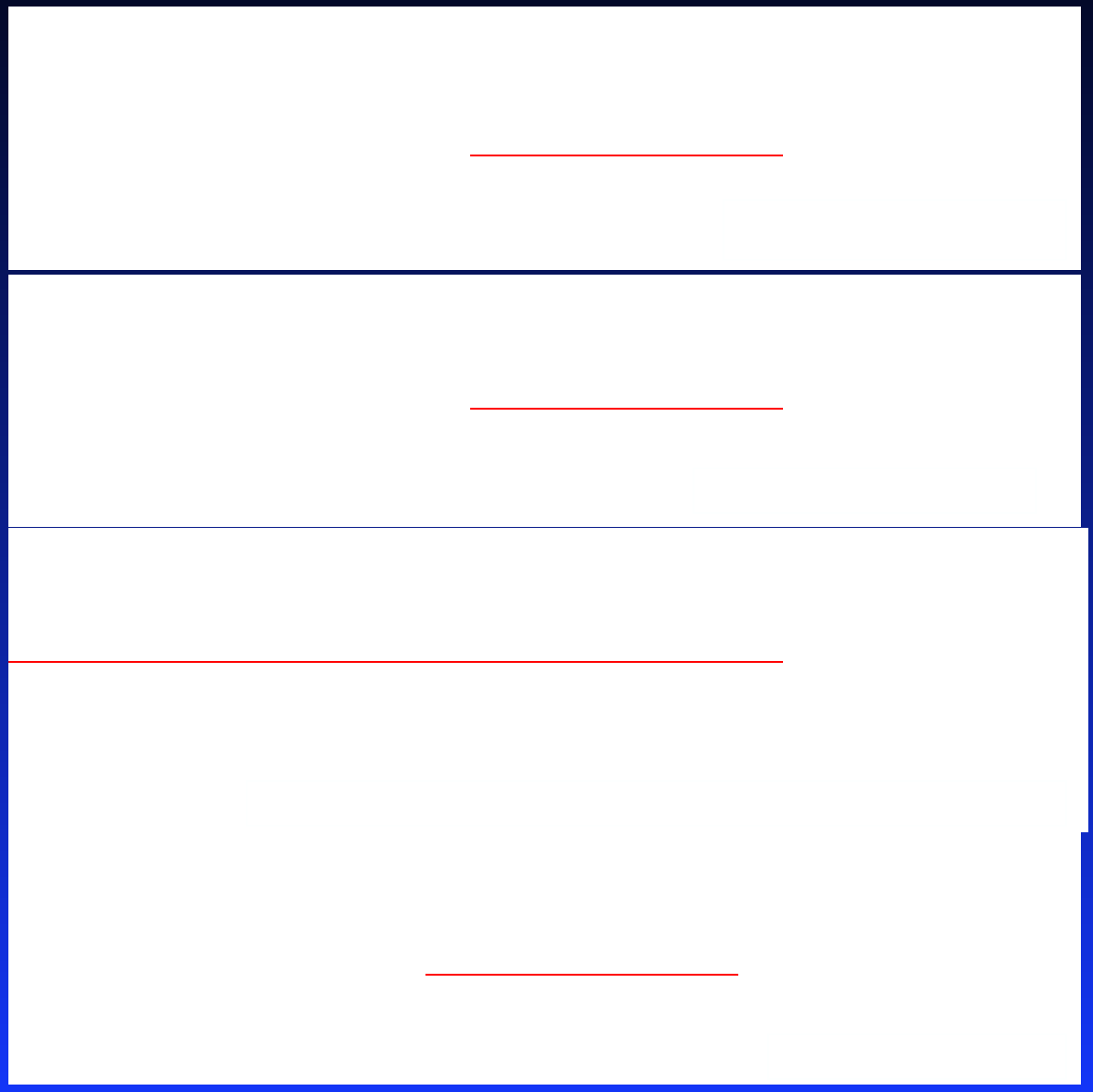
Double-blind RCT – 4 treatment groups x 52 weeks of Rx:

1. Lupron 3.75 mg monthly
2. Lupron 3.75 mg monthly plus norethindrone acetate 5 mg daily
3. Lupron 3.75 mg monthly plus norethindrone acetate 5 mg daily plus conjugated equine estrogens (CEE) 0.625 mg daily
4. Lupron 3.75 mg monthly plus norethindrone acetate 5 mg daily plus CEE 1.25 mg daily

M92-878 BMD

Here is what the raw data shows

M92-878 Efficacy



M92-878 Efficacy

‘half-life’ of pain relief after one year of Lupron:

2- 3 months!

This confirms the poor efficacy results of M90-471

Unimpressive results – why bother?

LUPRON REVIEW CONCLUSIONS

Lupron:

- is a safe drug with no side effects
- has no effect on BMD
- is better than surgery
- relieves pain in all patients
- cures endometriosis like menopause
- is a miracle drug

LUPRON REVIEW CONCLUSIONS

Lupron:

- is an unsafe drug with 100% side effects
- has greater BMD loss than published
- is not equal to surgery – endometriosis remains
- relieves pain temporarily in some patients
- does nothing to endometriosis like menopause
- is a miracle drug – it's a miracle it was approved
- Lupron should be taken off the market; criminal charges should be applied

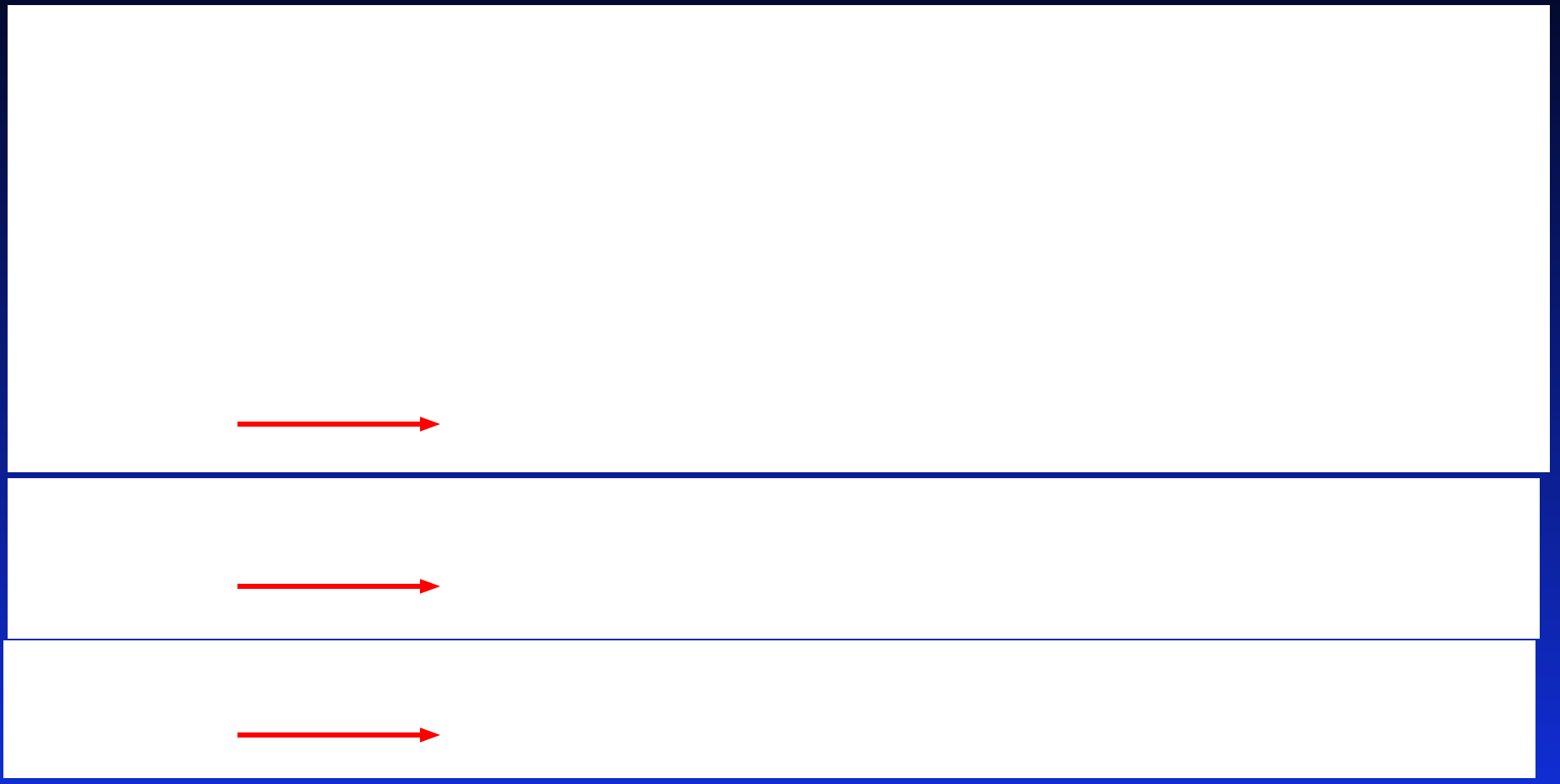
LUPRON

STOP USING IT!!!

ODAGIRBO

OBRIGADO

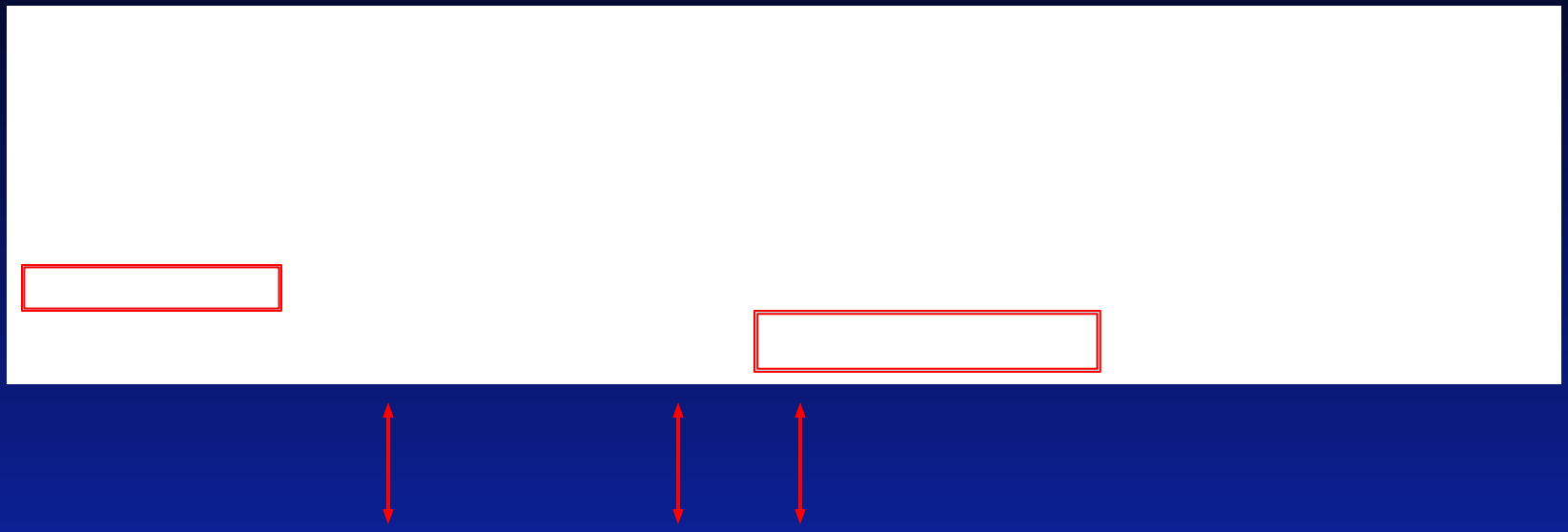
M92-878 Efficacy



Similar data handling occurred for Lupron + NE/CEE groups

M92-878 Efficacy

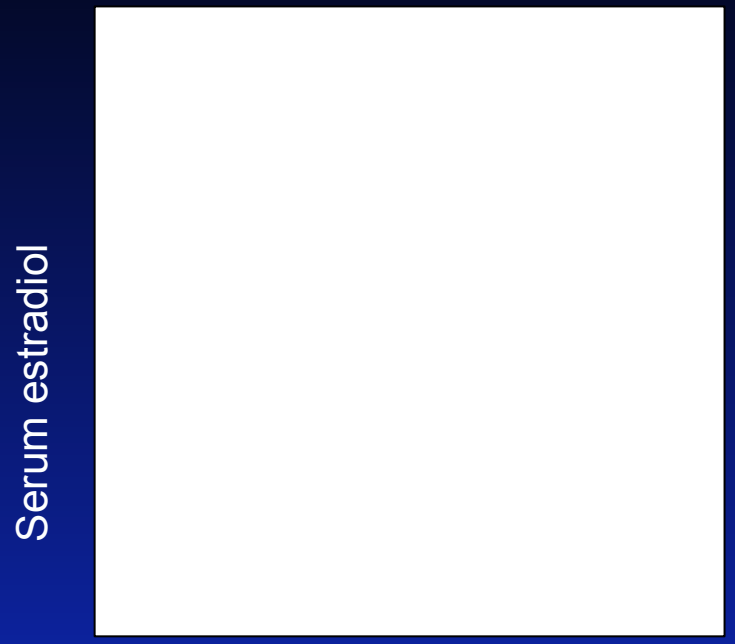
M86-039 (response of rAFS score at end of treatment)



Lupron	13.1	-	5.4 = 7.7 actual improvement
Danazol	14.2	-	5.5 = 8.7 actual improvement

Lesson: if your new drug efficacy is the same or worse than an existing drug, change arithmetic to favor your drug

M84-042 (estrogen)



Estradiol levels – pre-Rx and one month follow-up