**Presented**
**at the**
**Arthritis Advisory Committee Meeting**
**on**
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**by**

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# INTRODUCTION

loading dose, daily dose determinations - clinical extrapolation, PK modeling

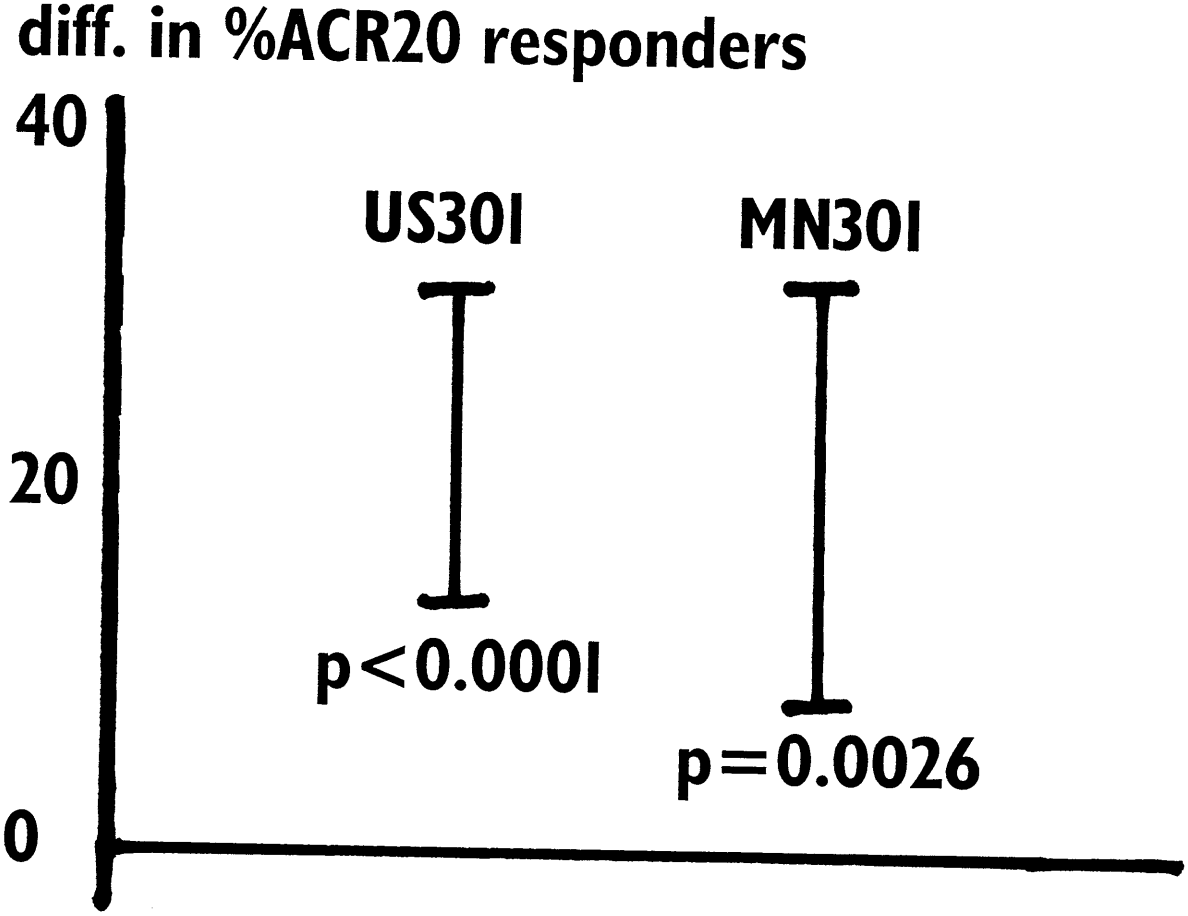
pivotal trial design protocols

| | | |
|---|---|---|
| US301 | LEF, MTX, PLC | 1 YR |
| MN301 | LEF, SSZ, PLC | 6MO |
| MN302 | LEF, MTX | 1 YR |

co-primary endpoints -- clinical/xray
disability/HR-QOL -- US301 only
difference/equivalence designs

US301 / MN302: demographics, folate use

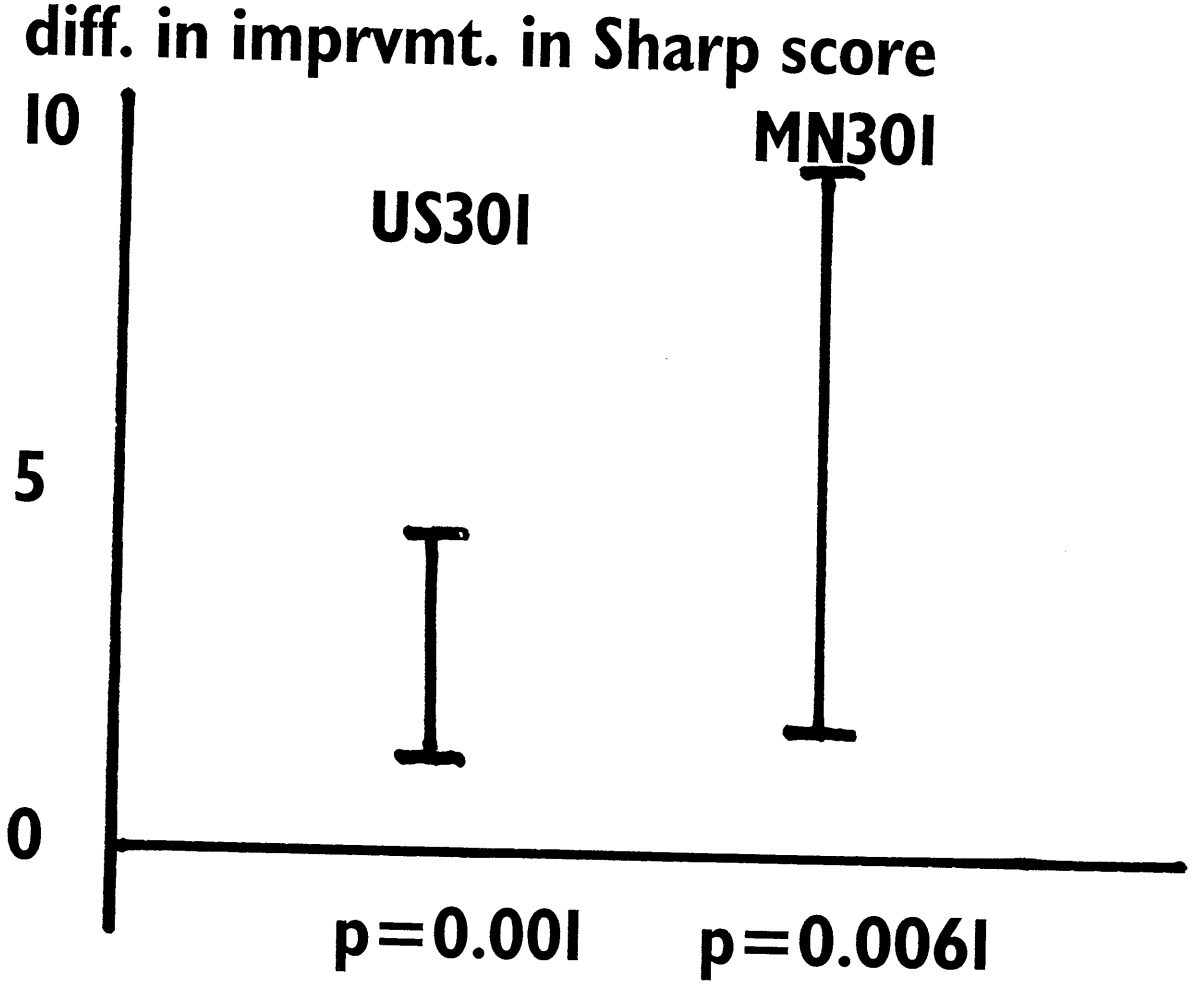
# EVIDENCE OF EFFICACY (CLIN.)
## (label, p7)
## UNCERTAINTY ESTIMATE* OF LEF-PLC




*Trial repeats would yield other CIs. The true difference, which is unknown, and, with certainty, unknowable, will be contained within 95% of these CIs.

# EVIDENCE OF EFFICACY (RADIOGR.)
(label, p8)

## UNCERTAINTY ESTIMATE* OF LEF-PLC



# EVIDENCE OF SAFETY (OVERALL)

## CUMULATIVE INCIDENCE OF SELECTED AES IN PLC. CONTROLLED TRIALS (%)

(See >3% AE table - pp 16-7, label)

| | | <3MO | <6MO | <9MO | <12MO |
|---|---|---|---|---|---|
| diarrhea | L | 23% | 26% | 31% | 32% |
| | P | 11 | 12 | 14 | 16 |
| | M | 16 | 19 | 21 | 22 |
| | S | 6 | 9 | 11 | 13 |
| abd pain | L | 7 | 10 | 13 | 14 |
| | P | 7 | 7 | 9 | 11 |
| | M | 10 | 13 | 17 | 19 |
| | S | 9 | 11 | 12 | 12 |
| naus/vom | L | 15 | 17 | 18 | 21 |
| | P | 13 | 14 | 17 | 20 |
| | M | 17 | 20 | 20 | 20 |
| | S | 21 | 22 | 26 | 26 |

# EVIDENCE OF SAFETY (LFTs)
(my review - p62)

## %PTS SHOWING THE FOLLOWING:

| | US301 | | | MN301 | | | MN302 | |
|---|---|---|---|---|---|---|---|---|
| | LEF | MTX | PLC | LEF | SSZ | PLC | LEF | MTX |
| **SGOT** | | | | | | | | |
| >1.2 | 21 | 14 | 8 | 11 | 13 | 4 | 16 | 36 |
| >2 | 8 | 7 | 3 | 2 | 4 | 1 | 4 | 13 |
| >3 | 2 | 1 | 2 | 2 | 4 | 0 | 1 | 6 |
| **SGPT** | | | | | | | | |
| >1.2 | 29 | 20 | 9 | 19 | 14 | 12 | 21 | 48 |
| >2 | 11 | 9 | 3 | 2 | 6 | 1 | 7 | 31 |
| >3 | 4 | 3 | 3 | 2 | 2 | 1 | 3 | 17 |

# EVIDENCE OF SAFETY (MALIG./LP DIS.)
(label, pII)

## CASES PER 1000 PATIENT-YEARS

| | LEF | PLC | MTX | SSZ |
|---|---|---|---|---|
| MALIGNANCIES | 9.6 | 11.5 | 19.4 | 9.8 |
| L/P DISEASES | 2.2 | 0 | 1.4 | 15.0* |
| TOTAL PT-YRS | 2077 | 226 | 936 | 258 |

* Very wide CIs with small denomenators, and have ("120d Update") 2 more SSZ cases.

# EVIDENCE OF SAFETY (METABOLIC)

mean changes in plc. controlled trials

| | Lef | Plc |
|---|---|---|
| uric acid (umol/l) | -61.41 | 1.37 |
| calcium (mmol/l) | -0.01 | 0.01 |
| phosphorus (mmol/l) | -0.13 | 0.01 |
| creatinine (umol/l) | 0.36 | 0.28 |
| urea nitrogen (mmol/l) | -0.35 | 0.00 |

1yr (NDA) and 2yr ("120d Update") data fail to reveal any clinical consequences hypothesized as due to the above: eg. no renal events, no excess fractures.

# EVIDENCE OF SAFETY (MISC. SERIOUS AES)

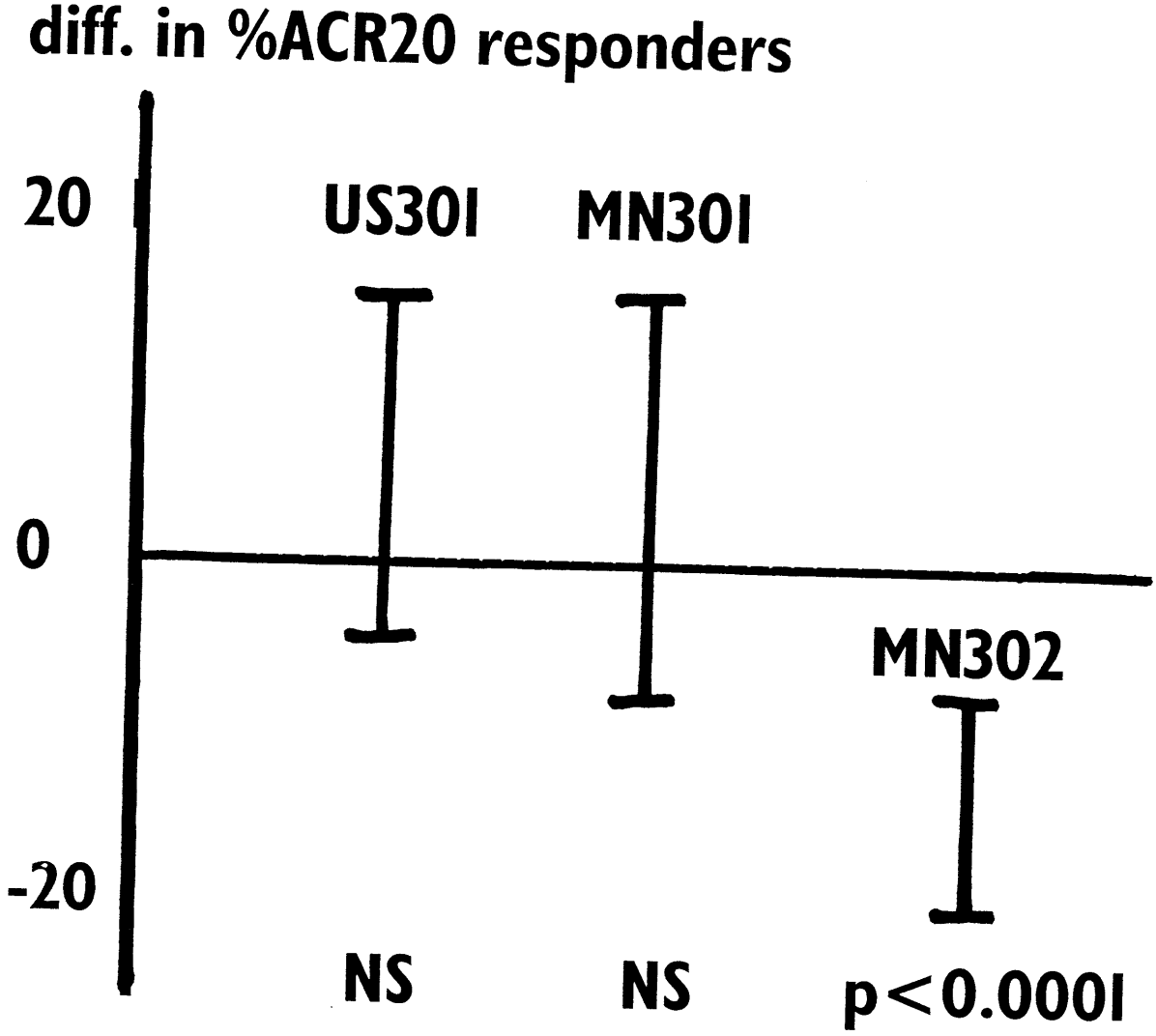
No clearcut serious hematologic toxicity (WBC<2K, PLT<100K, agranulocytosis)

No interstitial lung disease

No progressive renal insufficieny

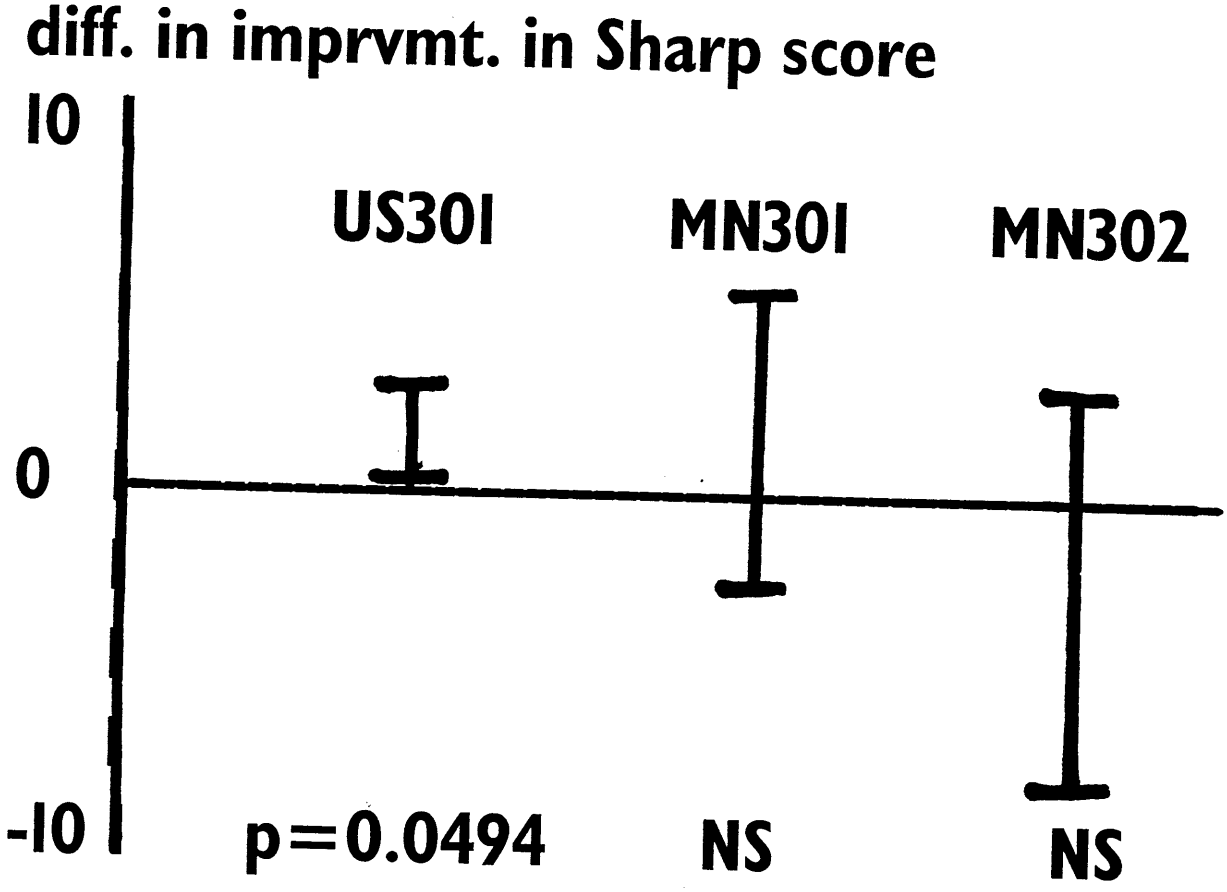
# UTILITY ----> LABELLING (CLIN.)

## UNCERTAINTY ESTIMATE*
## LEF-MTX, LEF-SSZ
## (label, p7)



# UTILITY ---> LABELLING (RADIOGR.)

## UNCERTAINTY ESTIMATE*
## LEF-MTX, LEF-SSZ
## (label, p8)

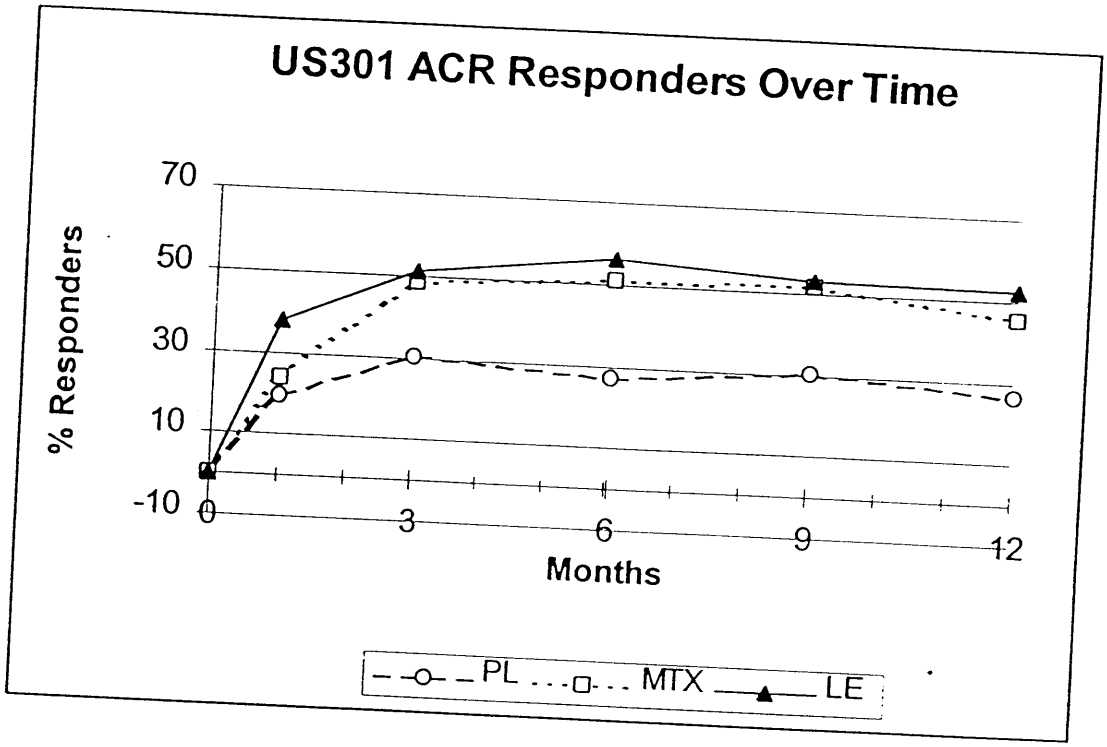


# COMPARATIVE SAFETY - LFTs
(label, p10)
(US301:L=M=182;MN302:L=501,M=498)

| | ALT(SGPT) | | | | AST(SGOT) | | | |
|---|---|---|---|---|---|---|---|---|
| | US301 | | MN302 | | US301 | | MN302 | |
| #X2-3 | L | M | L | M | L | M | L | M |
| 0-3mo | 6 | 6 | 11 | 16 | 9 | 5 | 7 | 9 |
| 3-6mo | 4 | 3 | 4 | 22 | 0 | 3 | 2 | 14 |
| 6-9mo | 2 | 2 | 2 | 19 | 1 | 2 | 0 | 10 |
| 9-12mo | 0 | 1 | 5 | 17 | 1 | 1 | 3 | 3 |
| #>3X | L | M | L | M | L | M | L | M |
| 0-3mo | 6 | 1 | 7 | 27 | 2 | 0 | 3 | 10 |
| 3-6mo | 1 | 3 | 1 | 34 | 1 | 1 | 1 | 11 |
| 6-9mo | 1 | 1 | 0 | 16 | 1 | 0 | 0 | 8 |
| 9-12mo | 0 | 0 | 5 | 6 | 0 | 0 | 3 | 0 |

note: virtually all reversed to <2x (label)

# COMPARATIVE DURABILITY
## All time point analysis
## (label, p9)



# COMPARATIVE HEALTH STATUS

## 1. MHAQ SCORE

| | | conf. int. | p value |
|---|---|---|---|
| US301 | LEF VS MTX | (-0.30,-0.06) | 0.0027 |
| MN301 | LEF VS SSZ | (-0.28,-0.04) | 0.0088 |
| MN302 | LEF VS MTX | (0.02, 0.13) | 0.0118 |

## 2. PET SCORE

| | | | |
|---|---|---|---|
| US301 | LEF VS MTX | (-6.42, -1.85) | 0.0004 |

## 3. SF-36 SCORES

US301 - LEF stat. sig. better than PLC in 5/8 domains (all but mental health, role:phys, and role:emotional). LEF stat. sig. better than MTX in 2 domains (pain, vitality)

# EXPERIENCE WITH CO-USE WITH MTX
(label, p15; my review, p50)

Pilot 6mo clinical / PK study in 30 pts.
(dis dur=14yr, #failed DMARDs=2.9,
#TJC/SJC=17/16)

PK - no interaction

Clinical - 53% showed +ACR20 response

LFTs - 17/30 w/ inc >1.2X AST:
2 (w/ inc>3X) discontinued, w/
reversal to <1.2X.
15 continued: 12 reversed to
<1.2X, 3 remained >1.2X.

Liver bx - by ACR MTX criteria - n=3:
1 - Roegnik Gr. I; 2 - Roegnik Gr. IIIa

# PREGNANCY ADVICE

NO PRECEDENTS FOR CURRENT SITUATION: (I) KNOWN AND VERIFIABLE TARGET LEVEL, AND (2) CLINICAL STRATEGY TO ACHIEVE IT.

CROSS-DISCIPLINARY (PHARM., TERATOLOGY, PK, CLINICAL) ISSUE REGARDING PARADIGMS AND ASSUMPTIONS FOR EXTRAPOLATING EMBRYOTOXICITY DATA FROM ANIMALS TO HUMANS.

? PREGNANCY REGISTRY