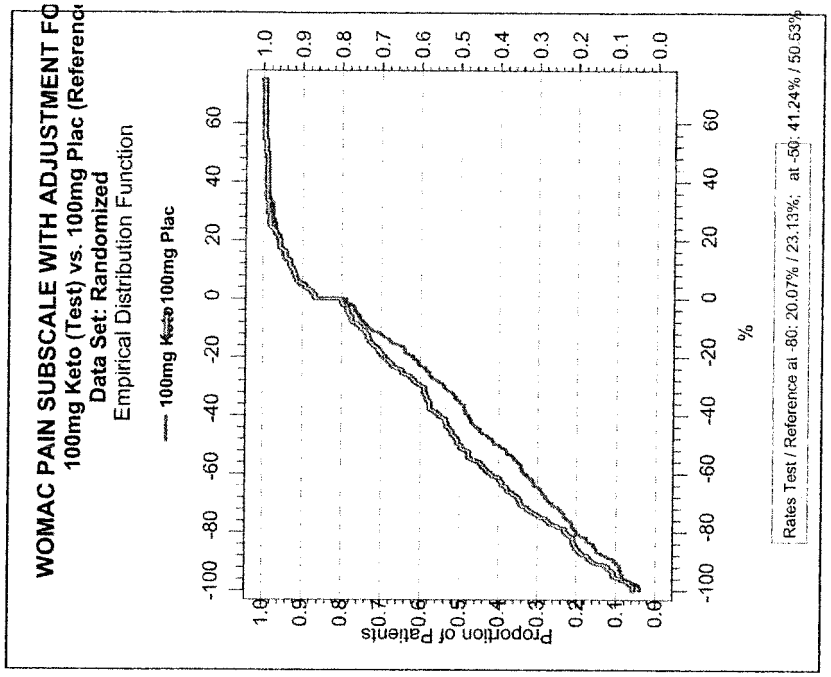
Pain - Mann-Whitney statistics and continuous responder analysis



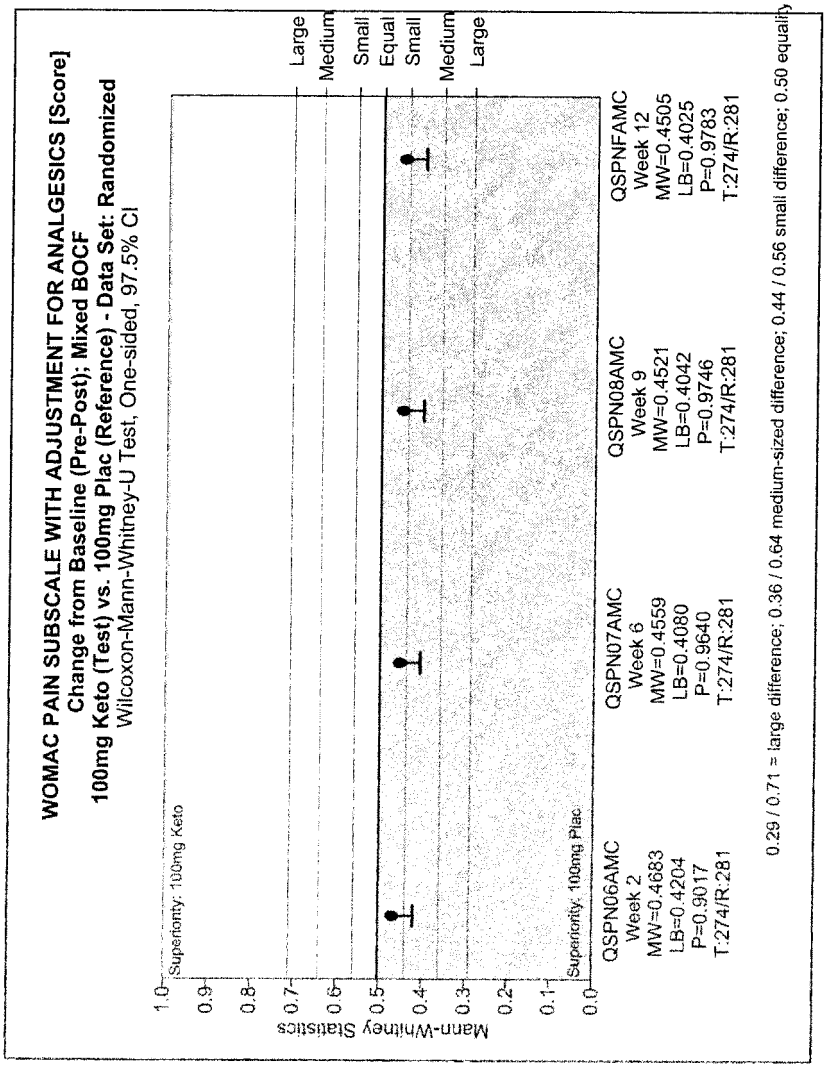


Figure 1

AEs by System Organ Class (SOC)

Drug Related Adverse Event by Organ CLass System; ITT Population

	Ketoprofen		Placebo	
	Absolute	Percent	Absolute	Percent
Eye Disorders	1	1,5	0	0,0
Gastrointestinal disorders	2	3,0	5	7,6
General disorders and administration site conditions	1	1,5	2	3,0
Injury, poisoning and procedural complications	2	3,0	0	0,0
Infections and infestations	0	0,0	1	1,5
Investigations	11	16,4	4	6,1
Musculoskeletal and connective tissue disorders	4	6,0	4	6,1
Nervous system disorders	5	7,5	9	13,6
Skin and subcutaneous tissue disorders	39	58,2	40	60,6
Vascular disorders	2	3,0	1	1,5
Total	67	100,0	66	100,0

Figure 2

Subgroup analysis for WOMAC pain intensity at baseline: > 5.5; ITT

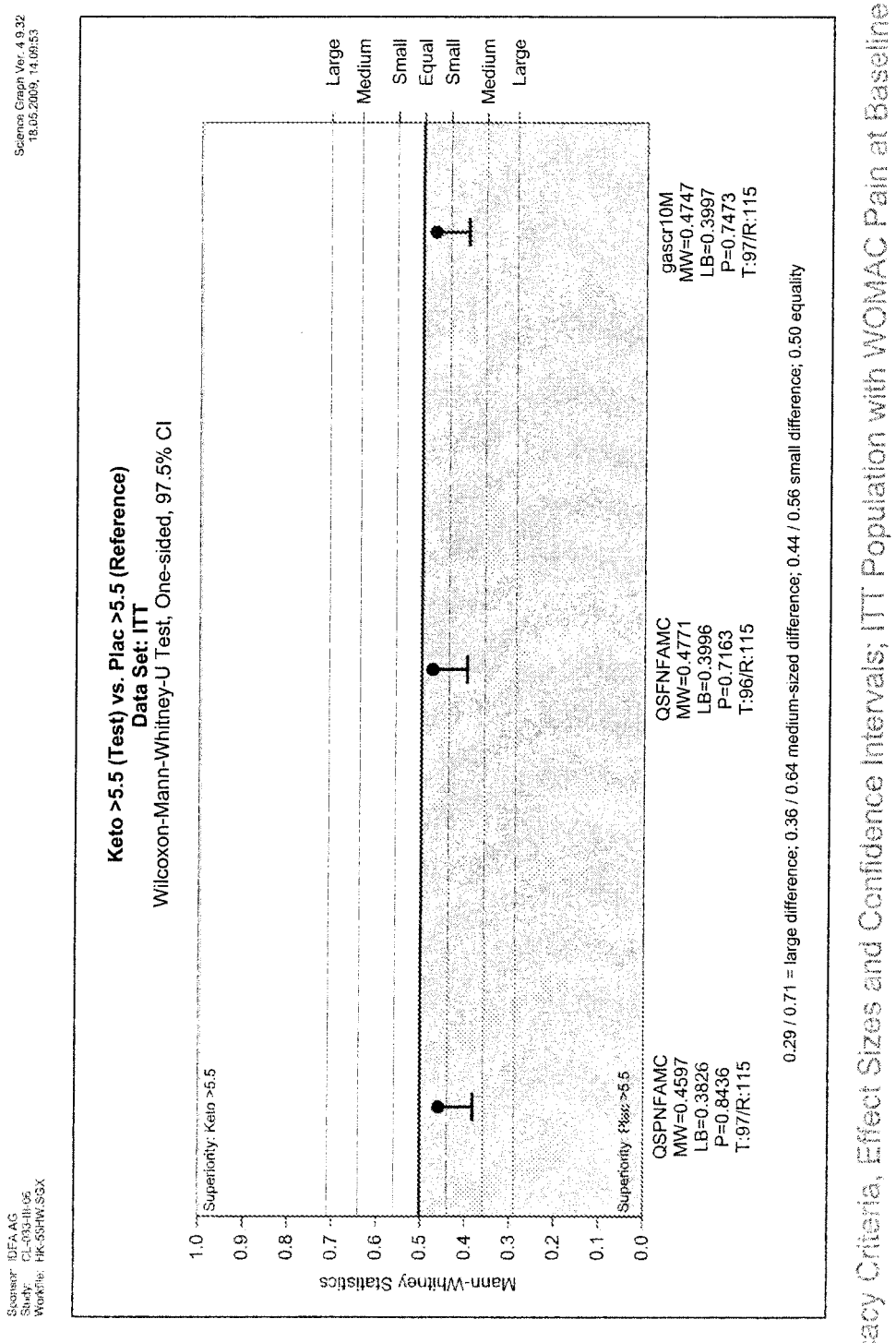


Figure 3

Primary Efficacy Criteria, Effect Sizes and Confidence Intervals; ITT Population with WOMAC Pain at Baseline > 5.5

Subgroup analysis for WOMAC pain intensity at baseline: ≤ 5.5; ITT

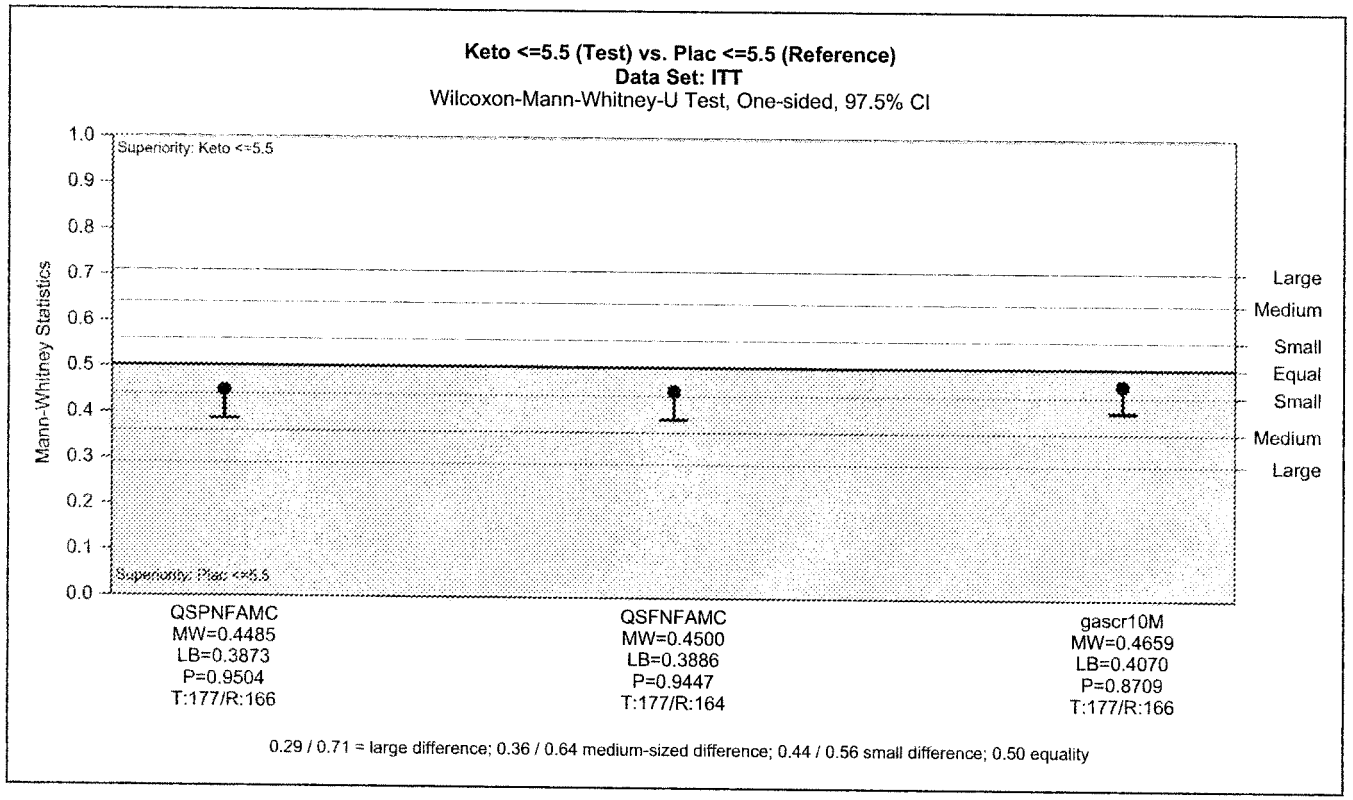


Figure 4

Primary Efficacy Criteria, Effect Sizes and Confidence Intervals; ITT Population with WOMAC Pain at Baseline ≤ 5.5

Use of rescue medication – Descriptive statistics

Intake of Analgesics during Treatment Period; ITT Population

CROSSTABULATION

Scores / Groups	No	Yes	Valid No.	Mean Rank
100mg Keto (N = 274)	49 17.88%	225 82.12%	274	279.874
100mg Plac (N = 281)	54 19.22%	227 80.78%	281	276.173

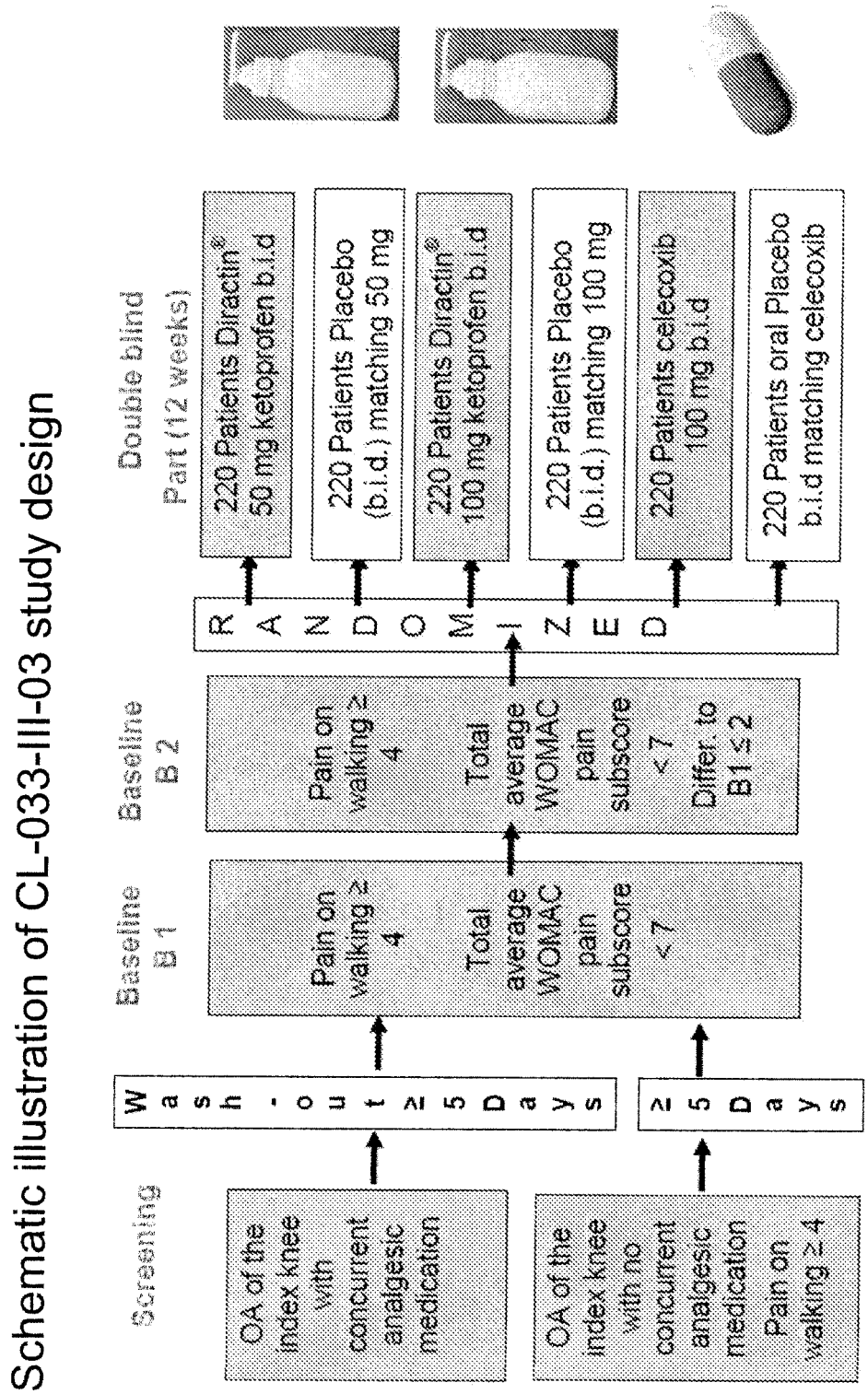
%: row percent

Mean Intake of Analgesics (Days); ITT Population

Descriptive Statistics

Groups	Mean	Valid No.
100mg Keto (N = 274)	13.1	274
100mg Plac (N = 281)	13.1	281

Figure 5


Schematic illustration of CL-033-III-03 study design
Screening
Baseline B 1
Baseline B 2
Double blind Part (12 weeks)
OA of the index knee with concurrent analgesic medication
OA of the index knee with no concurrent analgesic medication Pain on walking ≥ 4
Wash-out ≥ 5 Days
≥ 5 Days
Pain on walking ≥ 4
Total average WOMAC pain subscore < 7
Pain on walking ≥ 4
Total average WOMAC pain subscore < 7
Differ. to B1 ≤ 2
RANDOMIZED
220 Patients Diractin® 50 mg ketoprofen b.i.d
220 Patients Placebo (b.i.d.) matching 50 mg
220 Patients Diractin® 100 mg ketoprofen b.i.d
220 Patients Placebo (b.i.d.) matching 100 mg
220 Patients celecoxib 100 mg b.i.d
220 Patients oral Placebo b.i.d matching celecoxib

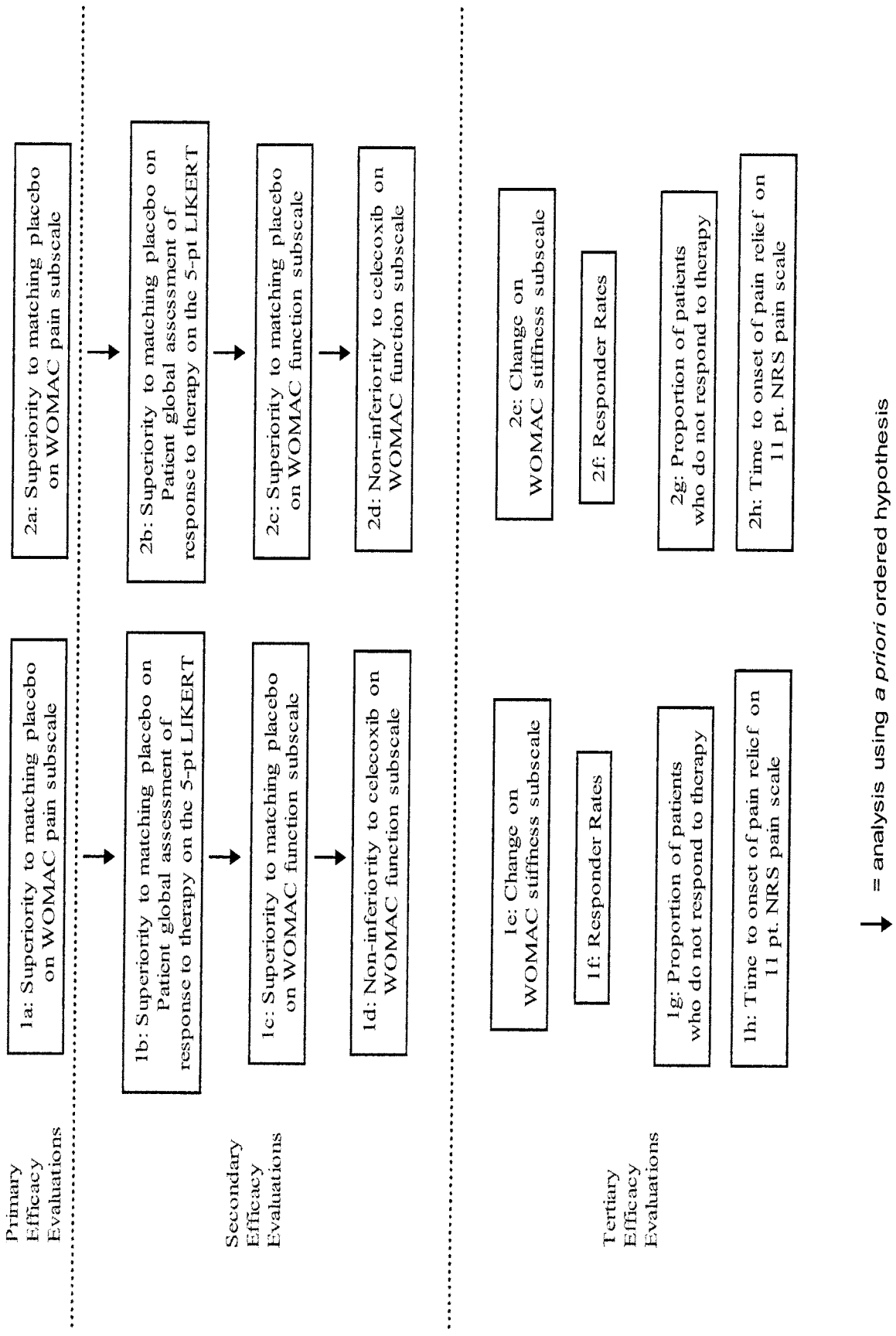
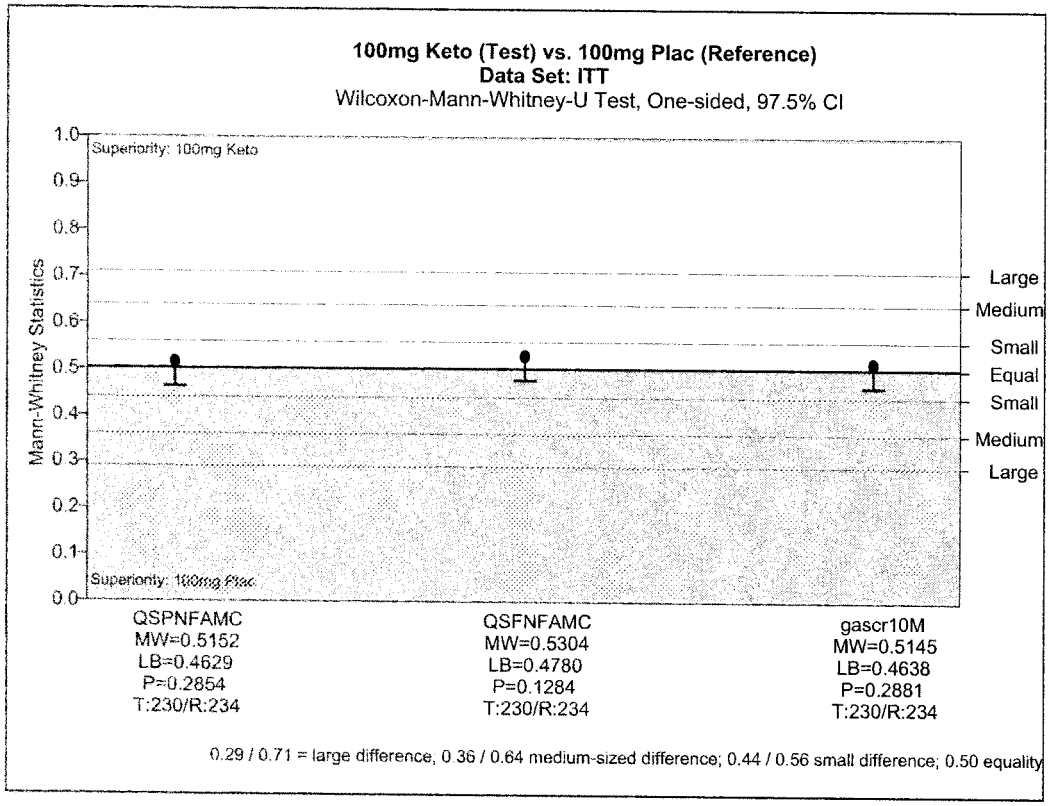
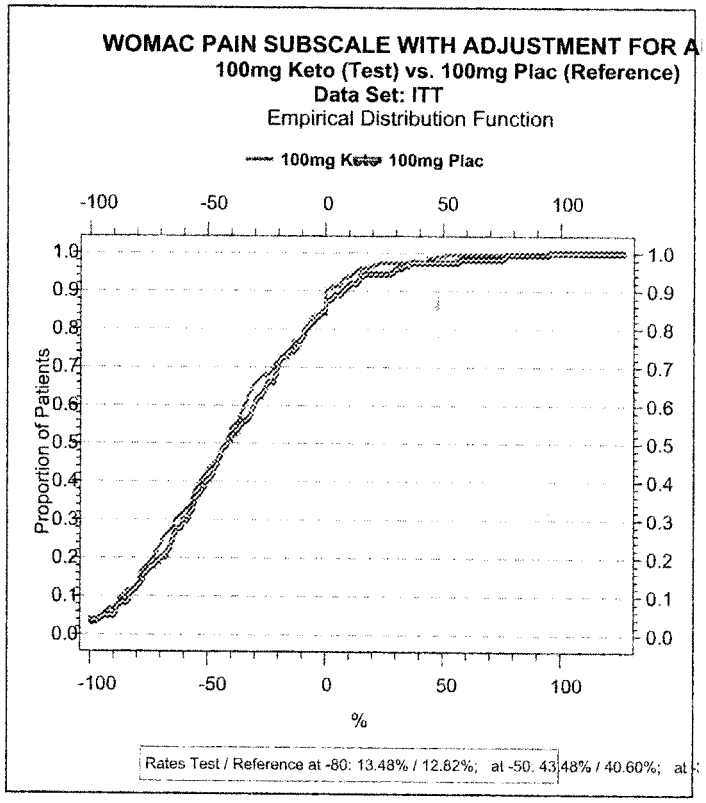

100 mg Diractin®
50 mg Diractin®
Primary Efficacy Evaluations
Secondary Efficacy Evaluations
Tertiary Efficacy Evaluations
1a: Superiority to matching placebo on WOMAC pain subscale
1b: Superiority to matching placebo on Patient global assessment of response to therapy on the 5-pt LIKERT
1c: Superiority to matching placebo on WOMAC function subscale
1d: Non-inferiority to celecoxib on WOMAC function subscale
1e: Change on WOMAC stiffness subscale
1f: Responder Rates
1g: Proportion of patients who do not respond to therapy
1h: Time to onset of pain relief on 11 pt. NRS pain scale
2a: Superiority to matching placebo on WOMAC pain subscale
2b: Superiority to matching placebo on Patient global assessment of response to therapy on the 5-pt LIKERT
2c: Superiority to matching placebo on WOMAC function subscale
2d: Non-inferiority to celecoxib on WOMAC function subscale
2e: Change on WOMAC stiffness subscale
2f: Responder Rates
2g: Proportion of patients who do not respond to therapy
2h: Time to onset of pain relief on 11 pt. NRS pain scale
= analysis using *a priori* ordered hypothesis

Figure 7

100 mg ketoprofen e.c.* *vs.* „100“ placebo e.c.: WOMAC pain, Mann-Whitney statistics, Intention To Treat (ITT) and continuous responder analysis



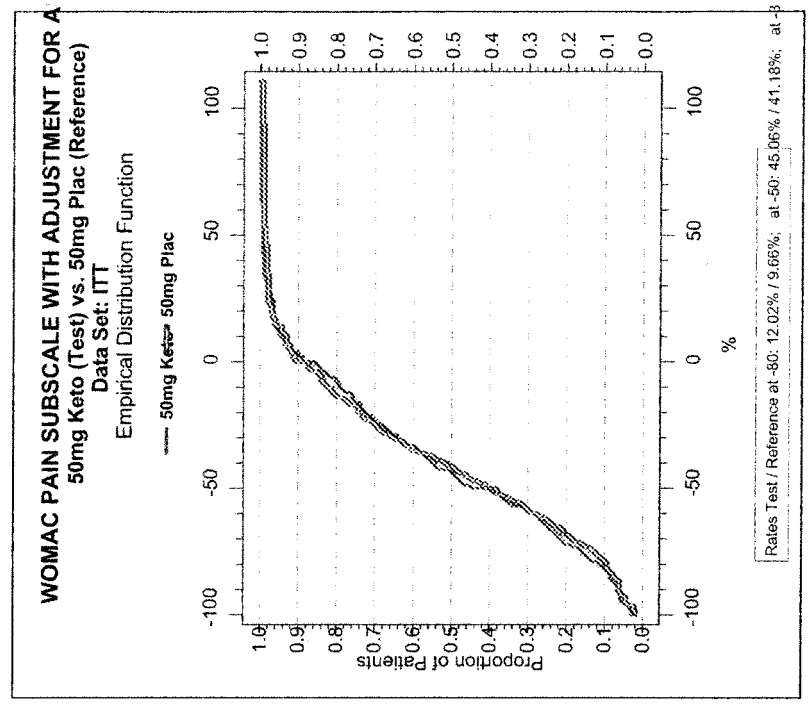


*Diractin® (IDEA)

Figure 8

SUBSTITUTE SHEET (RULE 26)

50 mg ketoprofen e.c. *vs.* „50“ placebo e.c.: WOMAC pain, Mann-Whitney statistics, ITT, and continuous responder analysis



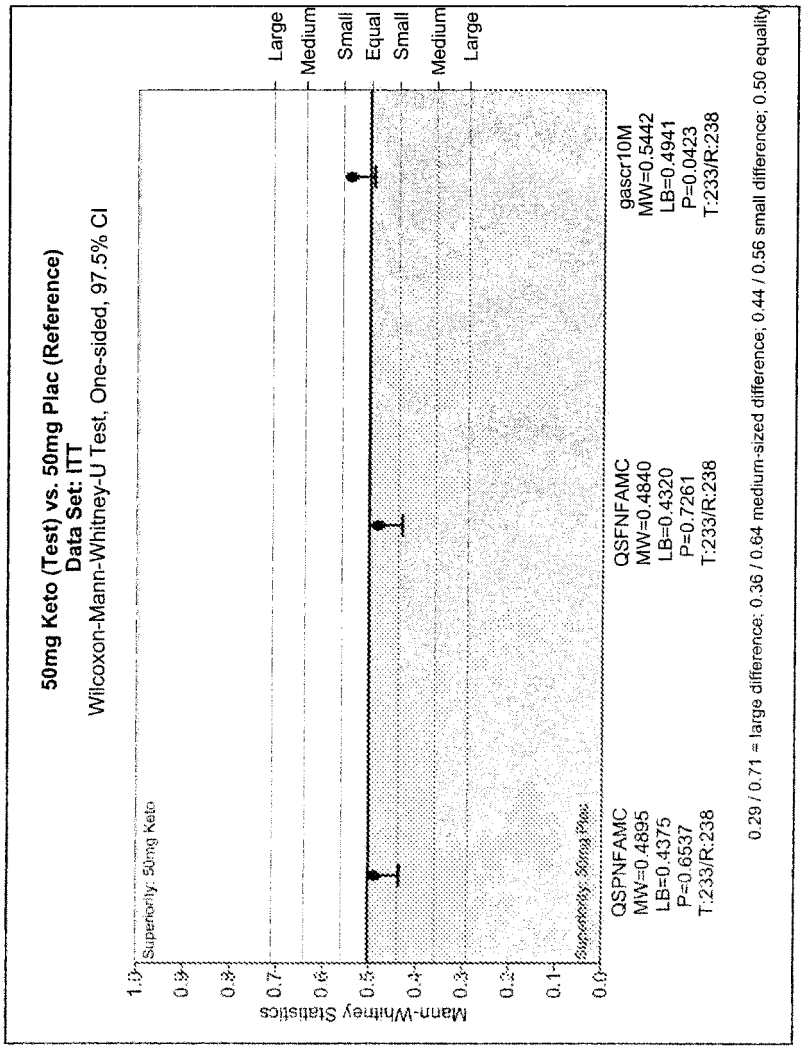


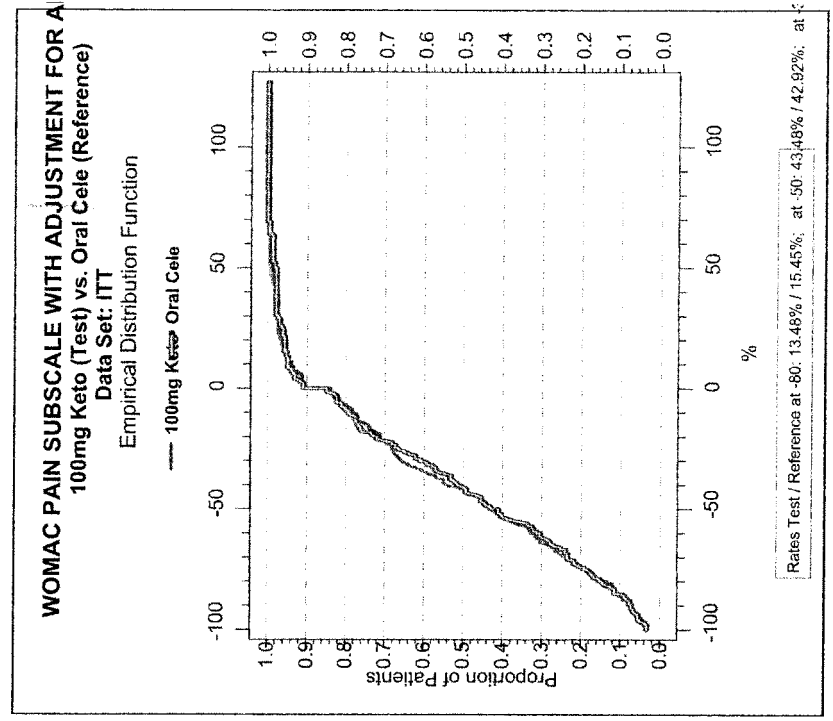
Figure 9

100 mg oral celecoxib* vs. „100“ oral placebo: WOMAC pain, Mann-Whitney statistics, ITT

*Celebrex® (Pfizer)

Figure 10

100 mg ketoprofen e.c. vs. 100 mg oral Celebrex®: WOMAC pain, Mann-Whitney statistics, ITT, and continuous responder analysis



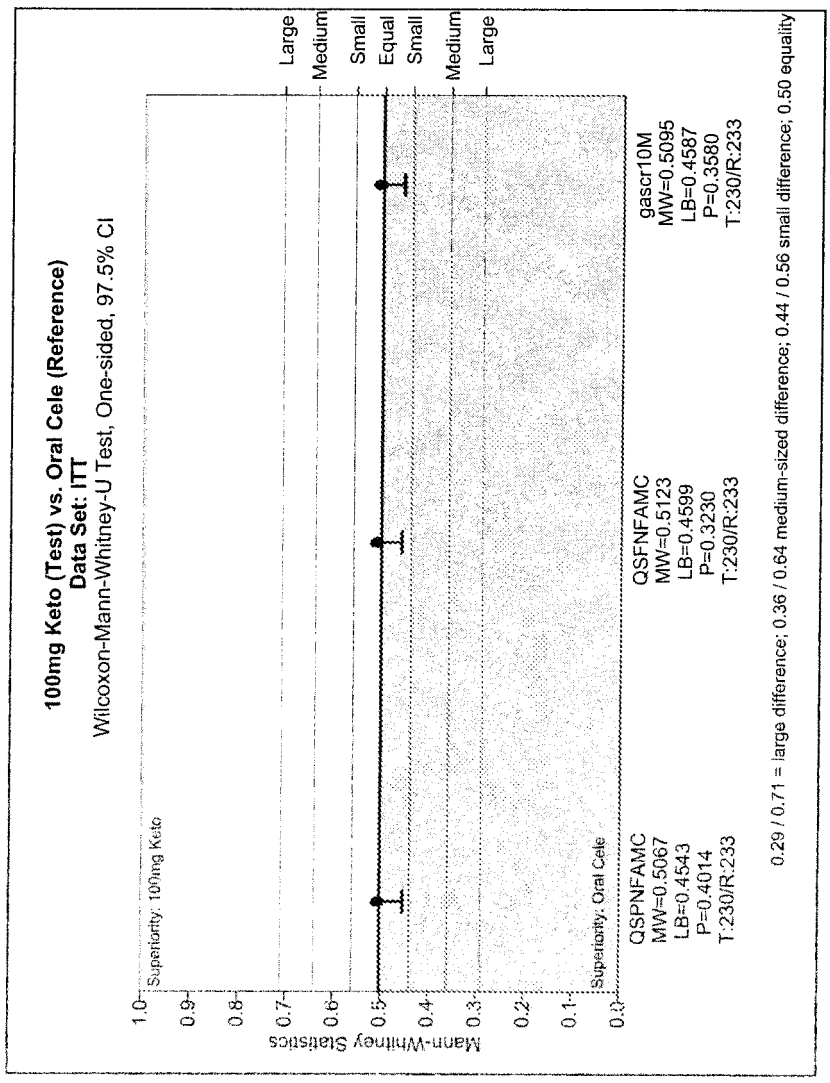


Figure 11

50 mg ketoprofen e.c. *vs.* 100 mg oral Celebrex®: WOMAC pain, Mann-Whitney statistics, ITT, and continuous responder analysis

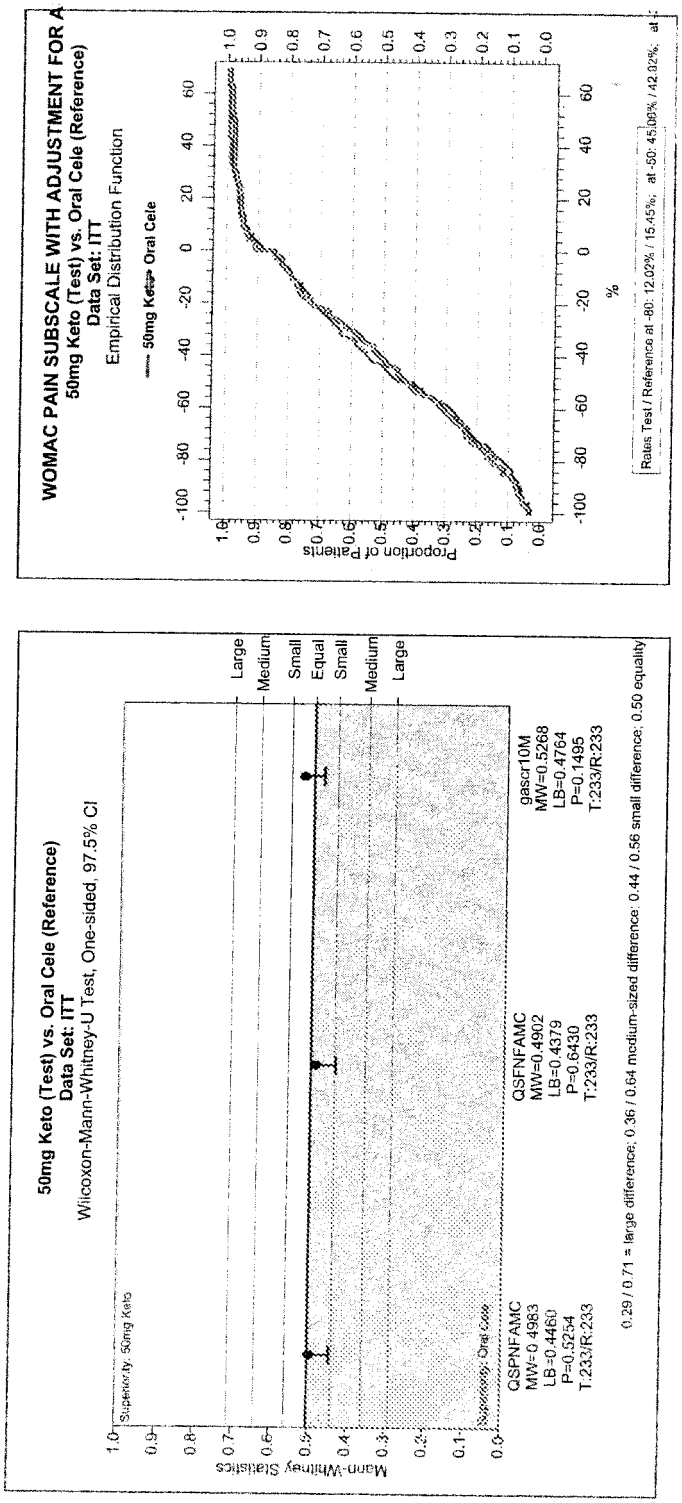


Figure 12

Results 100 mg ketoprofen e.c. vs. „100“ oral placebo: WOMAC pain, Mann-Whitney statistics, ITT

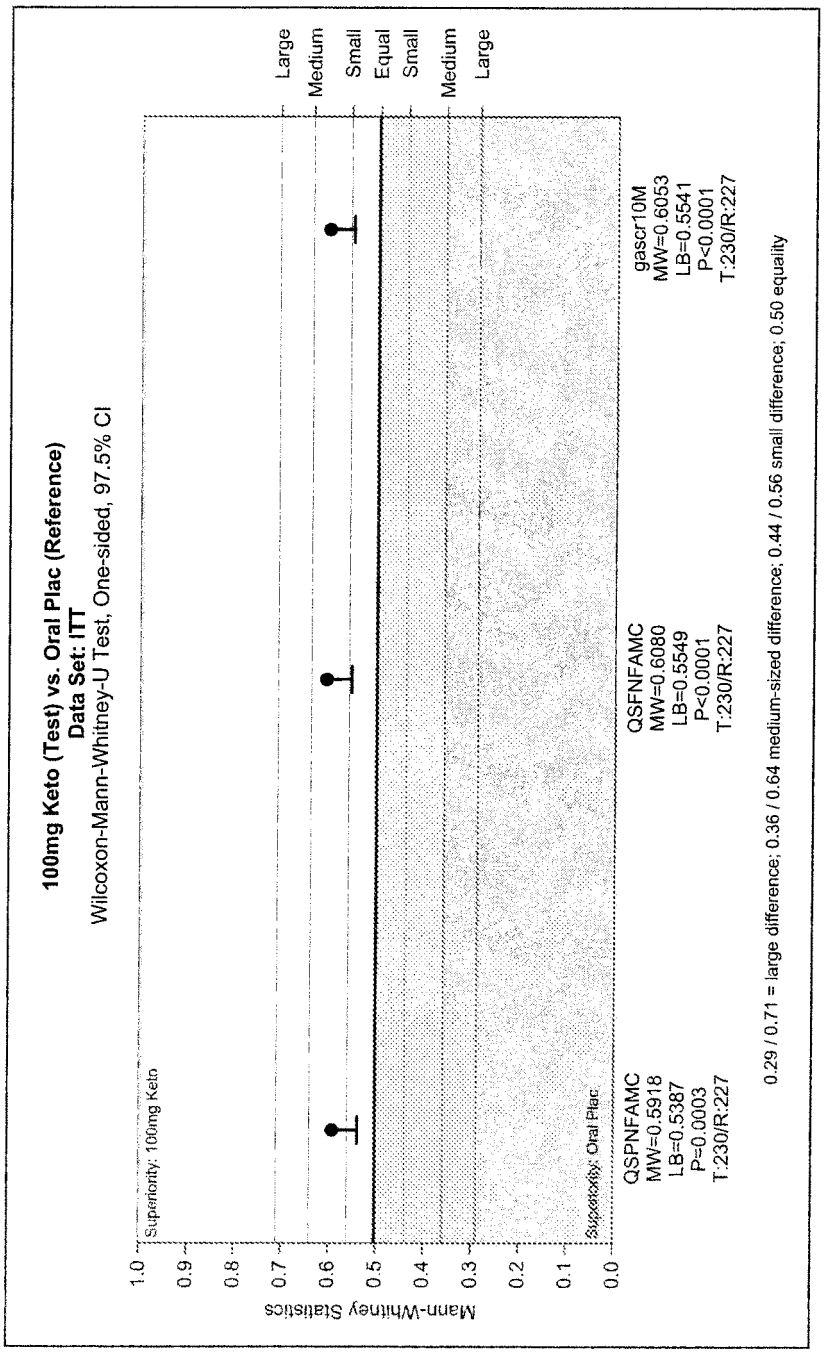


Figure 13

50 mg ketoprofen vs. „100“ oral placebo: WOMAC pain, Mann-Whitney statistics, ITT

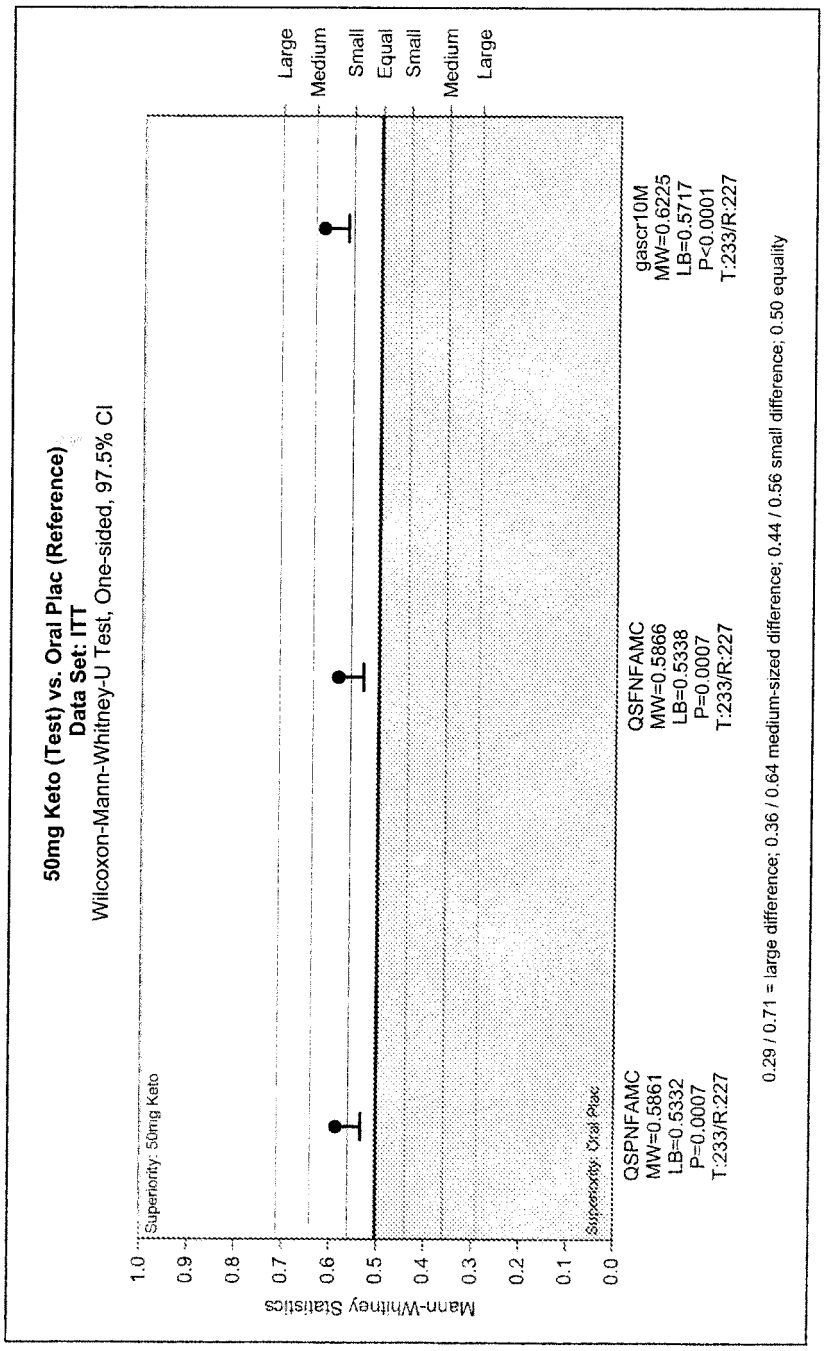


Figure 14

100 mg ketoprofen *vs.* 100 mg oral Celebrex®: WOMAC pain, Mann-Whitney statistics, per protocol (PP) population

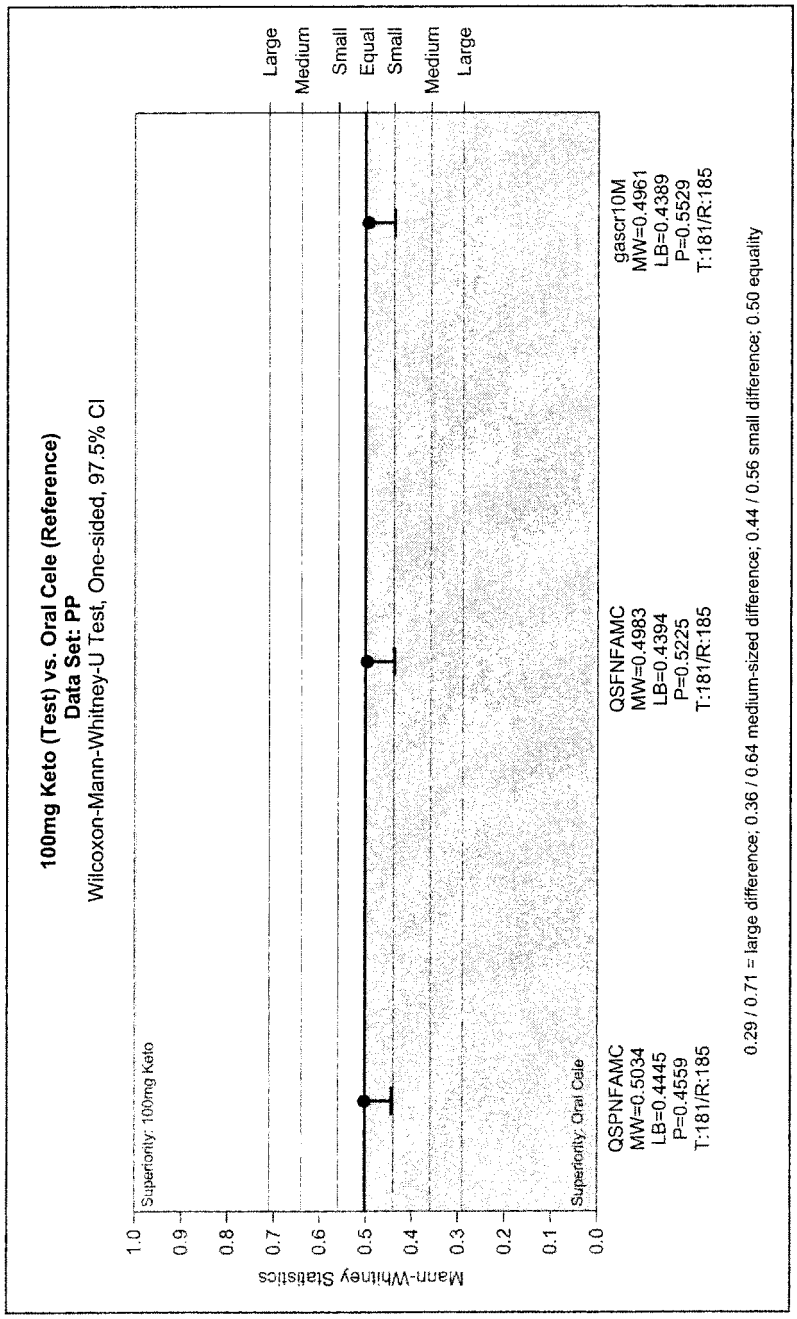


Figure 15

100 mg ketoprofen vs. „100“ oral placebo: WOMAC pain, Mann-Whitney statistics, per protocol population

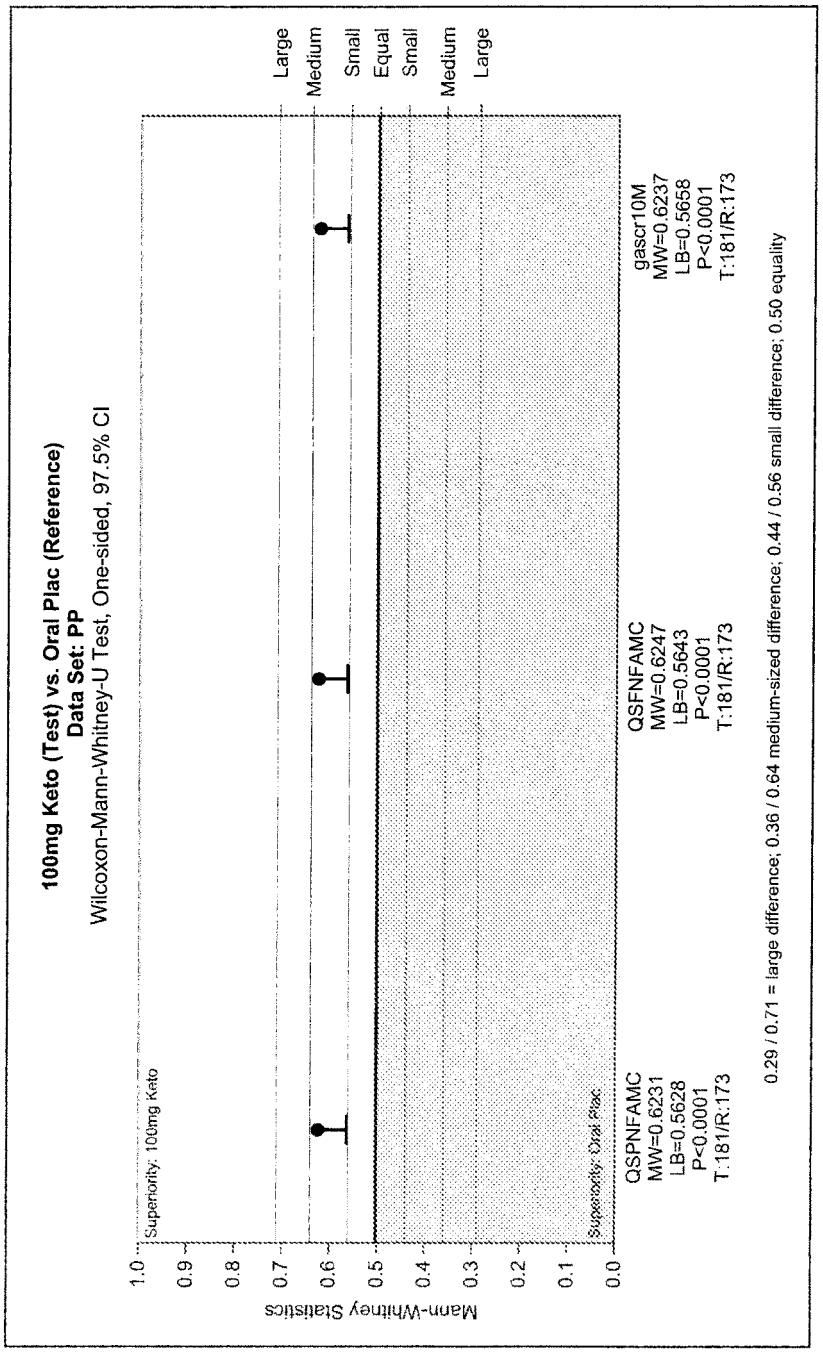


Figure 16

Possibly treatment related Aes by SOC (> 1% in any group)

	50mg Ketoprofen			50mg Placebo Gel			100mg Ketoprofen			100mg Placebo Gel			100mg Celecoxib			Oral Placebo		
	N=233			N=238			N=230			N=234			N=233			N=227		
Body System	AE	Pat	%	AE	Pat	%	AE	Pat	%	AE	Pat	%	AE	Pat	%	AE	Pat	%
Gastrointestinal	4	3	1.3	2	2	0.8	3	3	1.3	8	7	3.0	53	37	15.9	46	33	14.5
Nervous system				7	3	1.3				1	1	0.4	2	2	0.9	6	5	2.2
Skin/subcutaneous	19	13	5.6	16	14	5.9	33	28	12.2	28	26	11.1	5	5	2.1	2	2	0.9
Vascular	1	1	0.4	3	2	0.8				1	1	0.4	4	4	1.7	1	1	0.4

Figure 17

The average group-change from baseline for pain across studies [%]

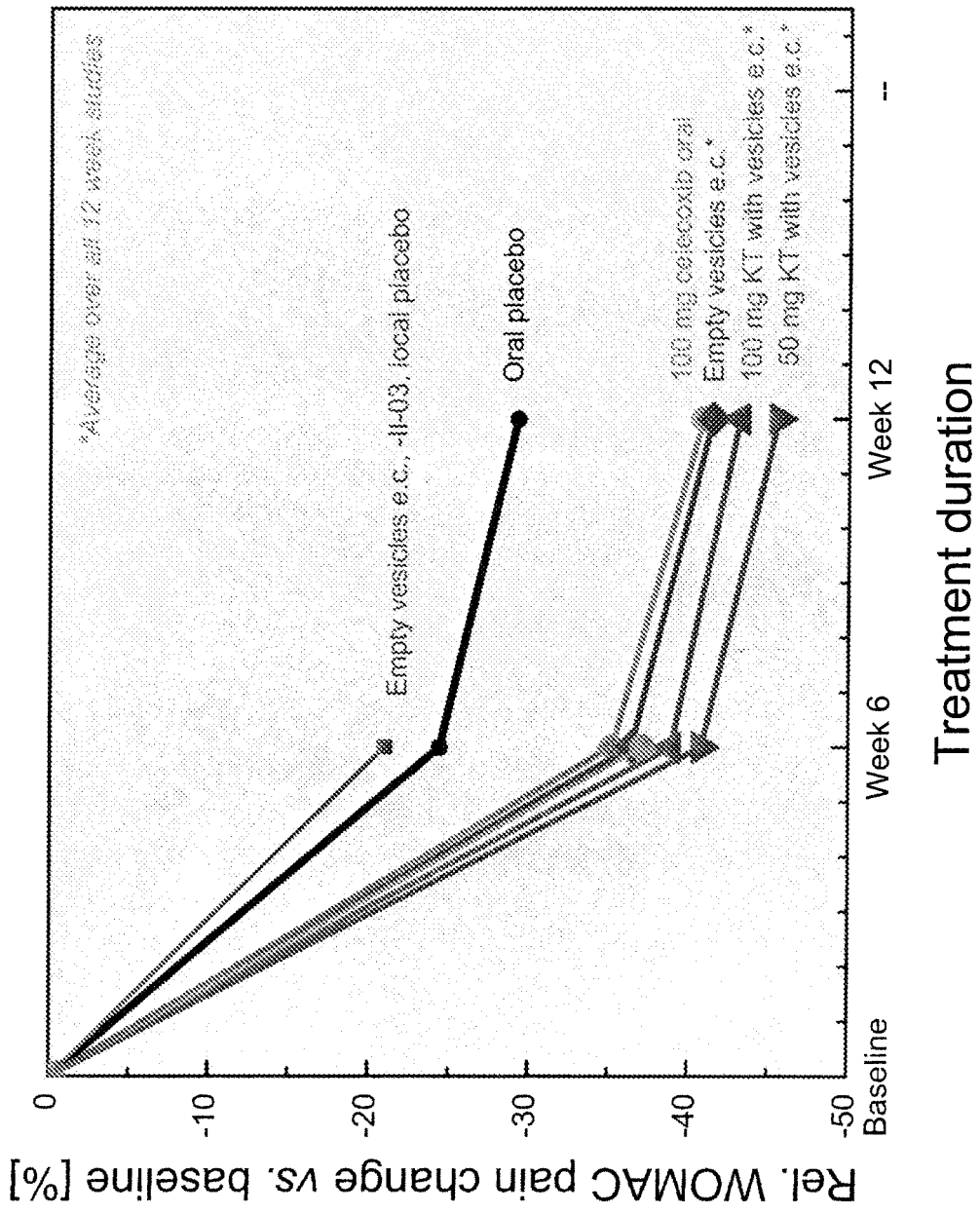


Figure 18

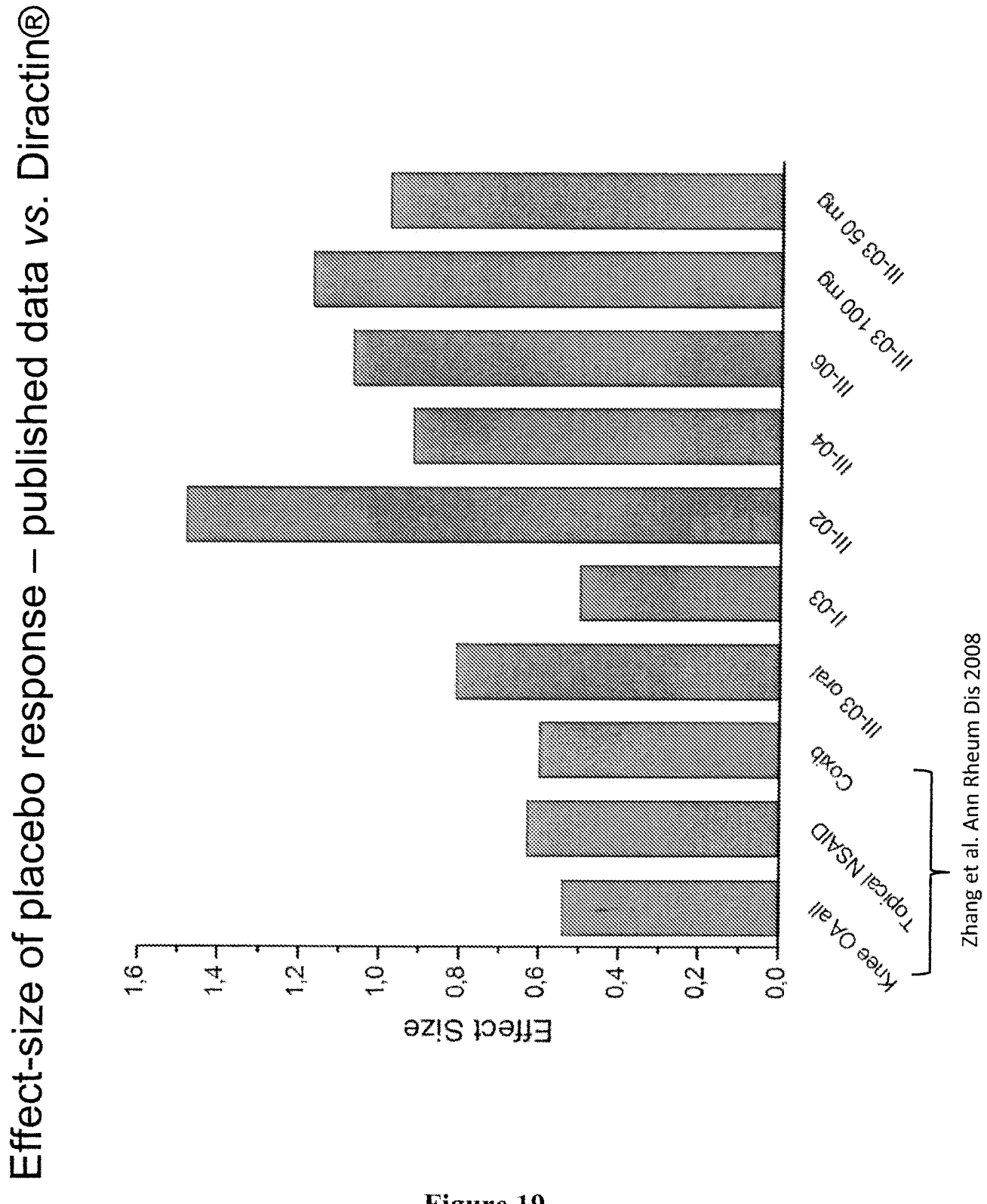

Effect-size of placebo response – published data vs. Diractin®
Effect Size
0,0
0,2
0,4
0,6
0,8
1,0
1,2
1,4
1,6
Knee OA all
Topical NSAID
Coxib
III-03 oral
II-03
III-02
III-04
III-06
III-03 100 mg
III-03 50 mg
Zhang et al. Ann Rheum Dis 2008

Figure 19

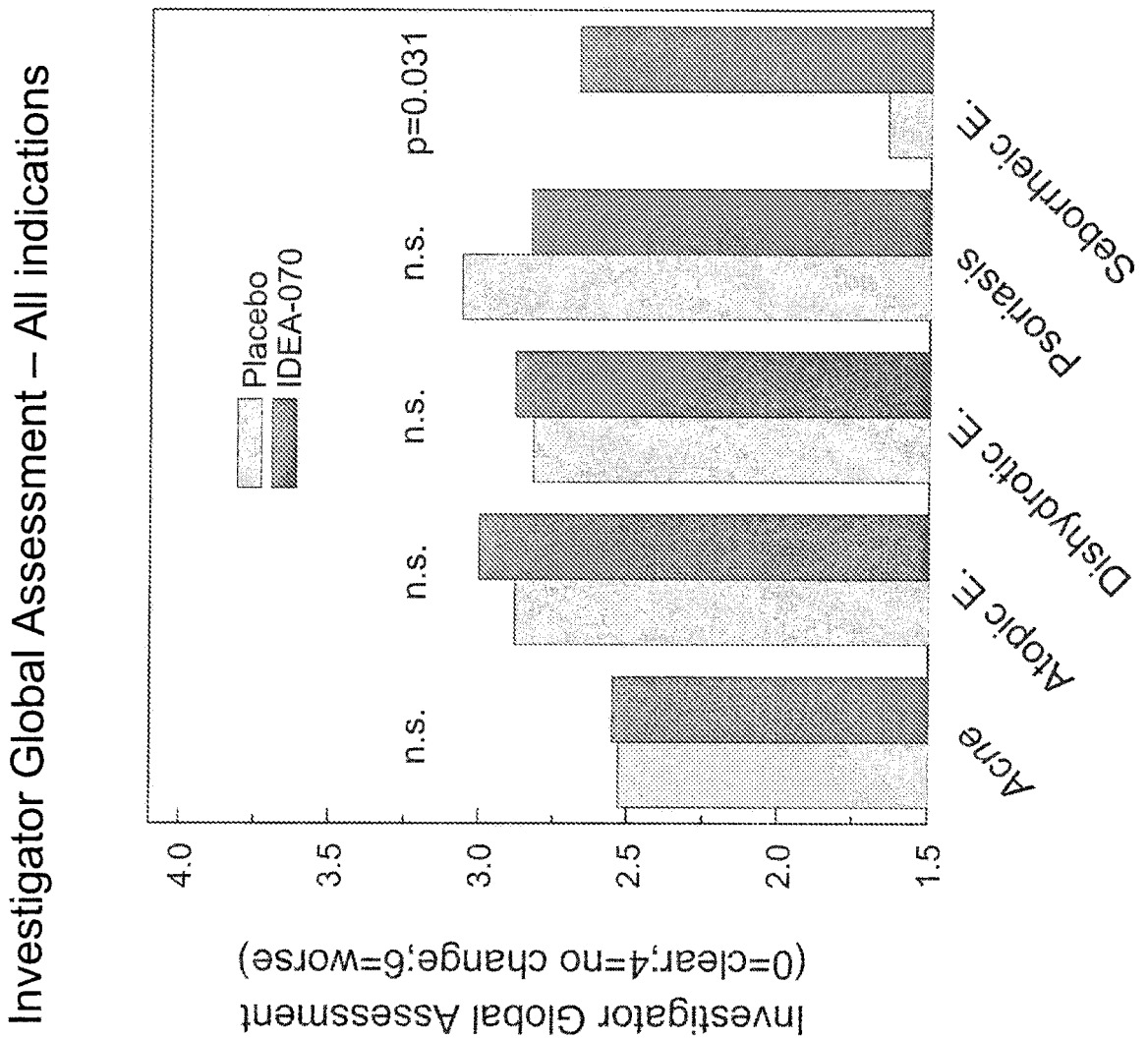

Investigator Global Assessment – All indications
Investigator Global Assessment
(0=clear;4=no change;6=worse)
4.0
3.5
3.0
2.5
2.0
1.5
Placebo
IDEA-070
n.s.
n.s.
n.s.
p=0.031
Acne
Atopic E.
Dishydrotic E.
Psoriasis
Seborrheic E.

Figure 20

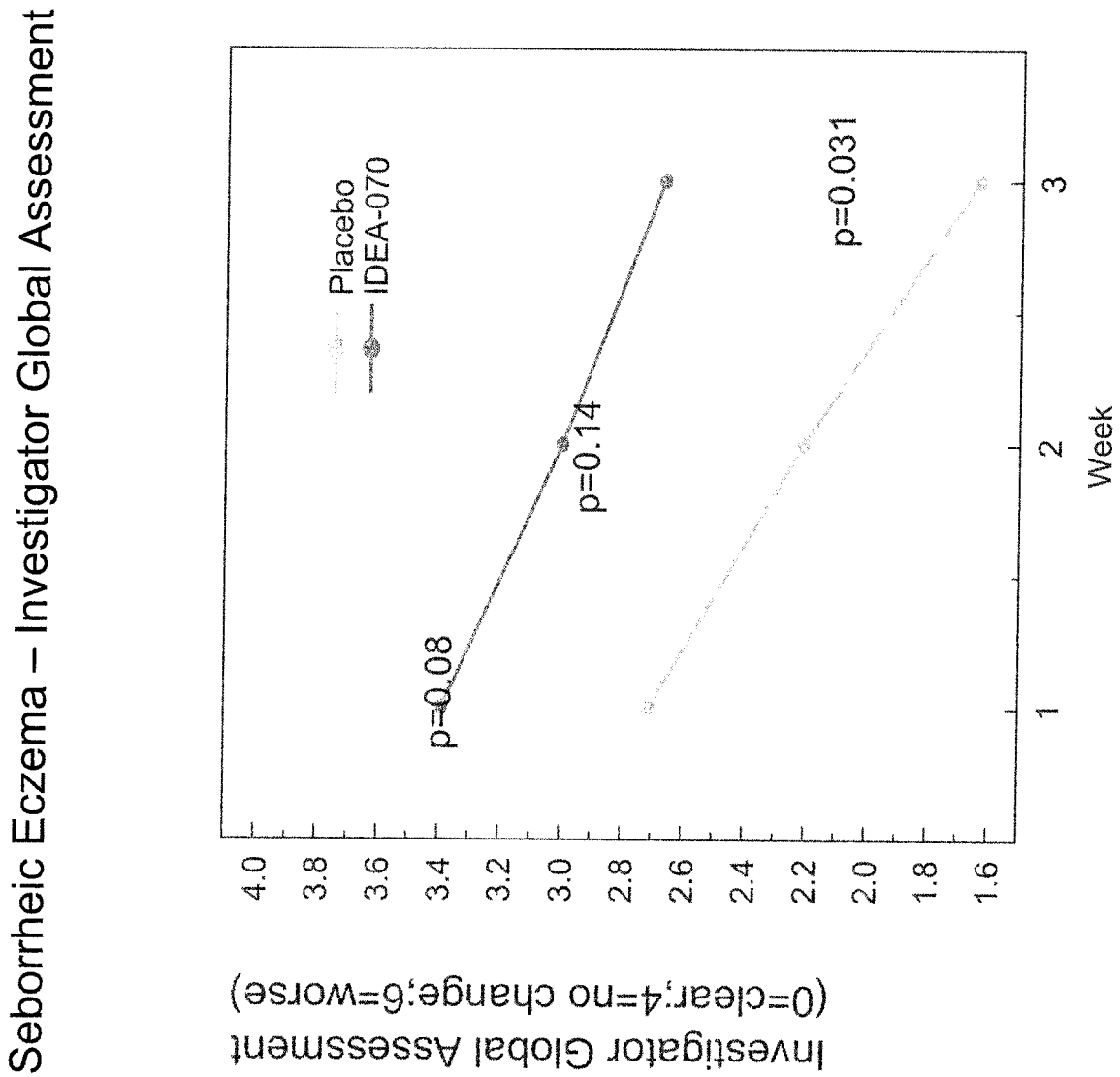

Seborrheic Eczema – Investigator Global Assessment
Investigator Global Assessment
(0=clear;4=no change;6=worse)
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1
2
3
Week
Placebo
IDEA-070
p=0.08
p=0.14
p=0.031

Figure 21

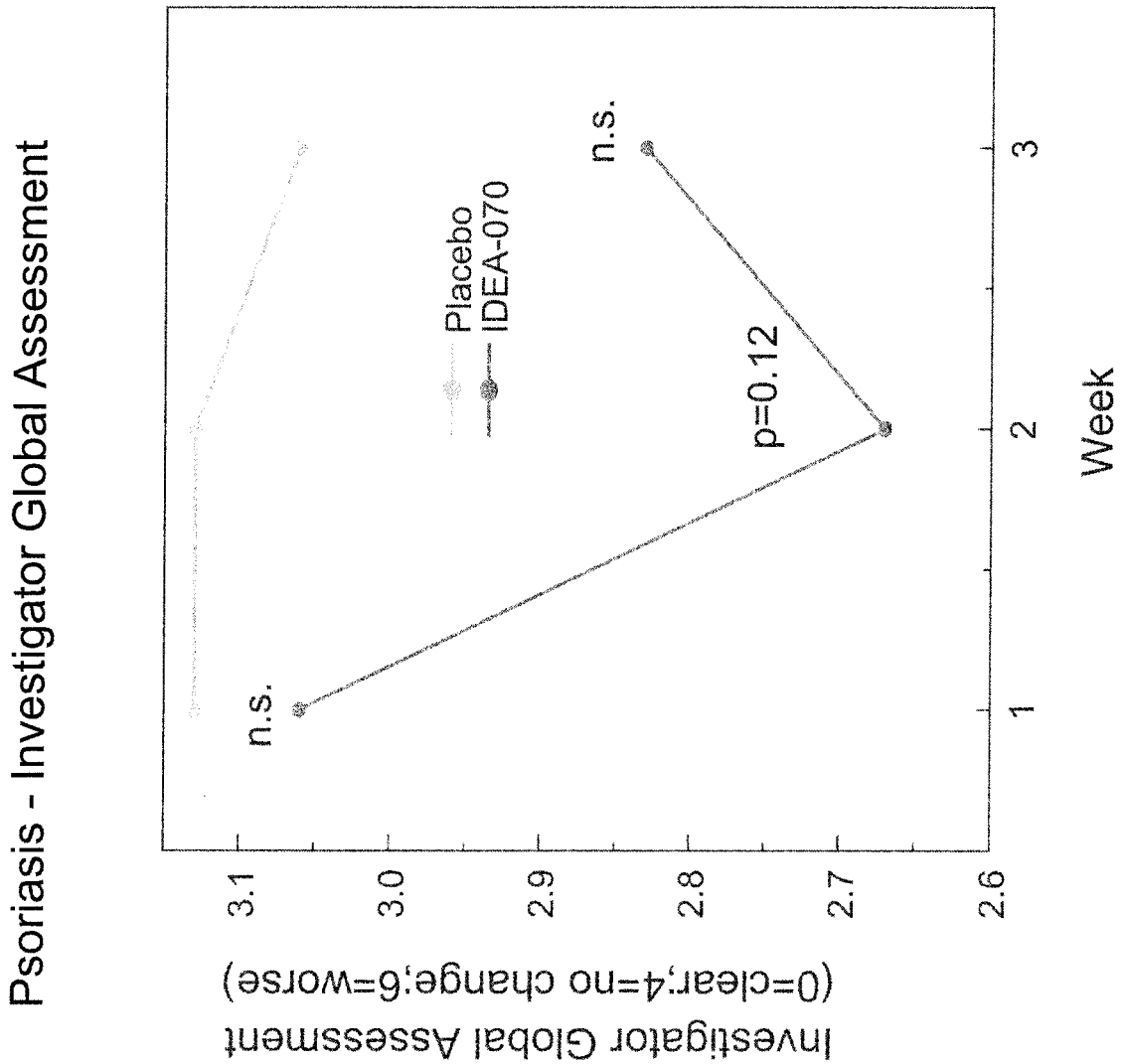

Psoriasis - Investigator Global Assessment
Investigator Global Assessment
(0=clear;4=no change;6=worse)
3.1
3.0
2.9
2.8
2.7
2.6
1
2
3
Week
Placebo
IDEA-070
n.s.
n.s.
p=0.12

Figure 22

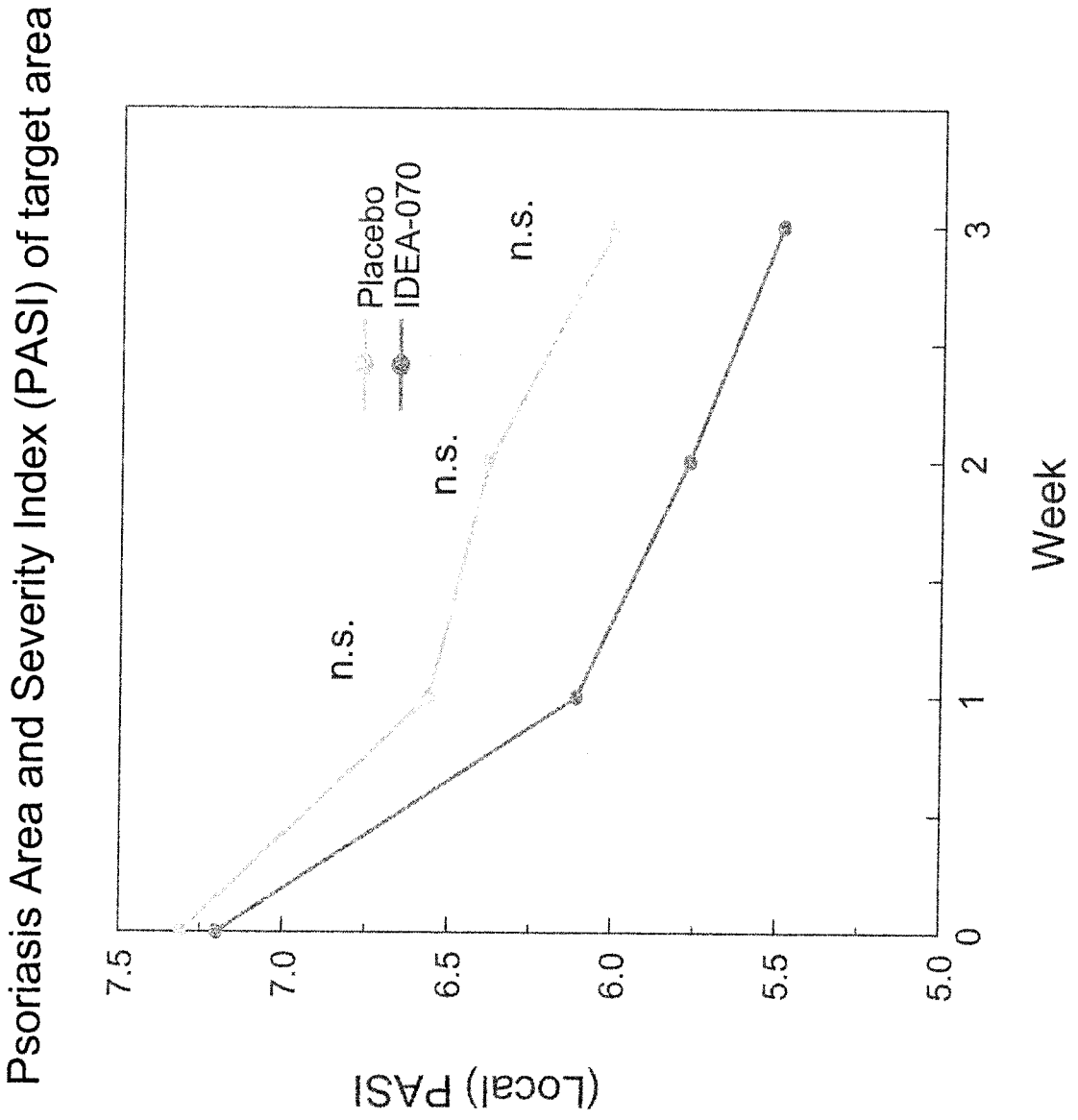

Psoriasis Area and Severity Index (PASI) of target area
(Local) PASI
7.5
7.0
6.5
6.0
5.5
5.0
0
1
2
3
Week
Placebo
IDEA-070
n.s.
n.s.
n.s.

Figure 23

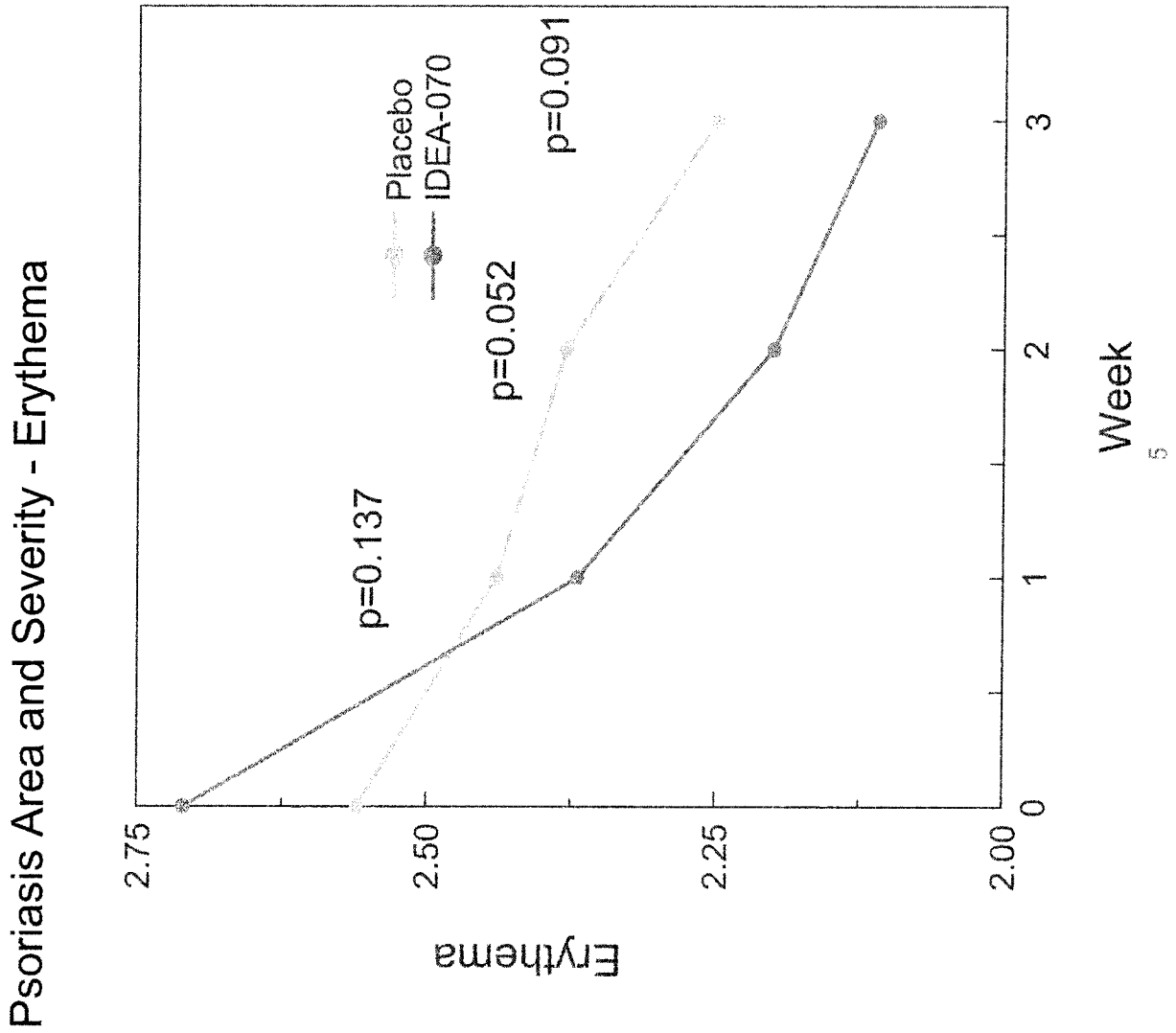
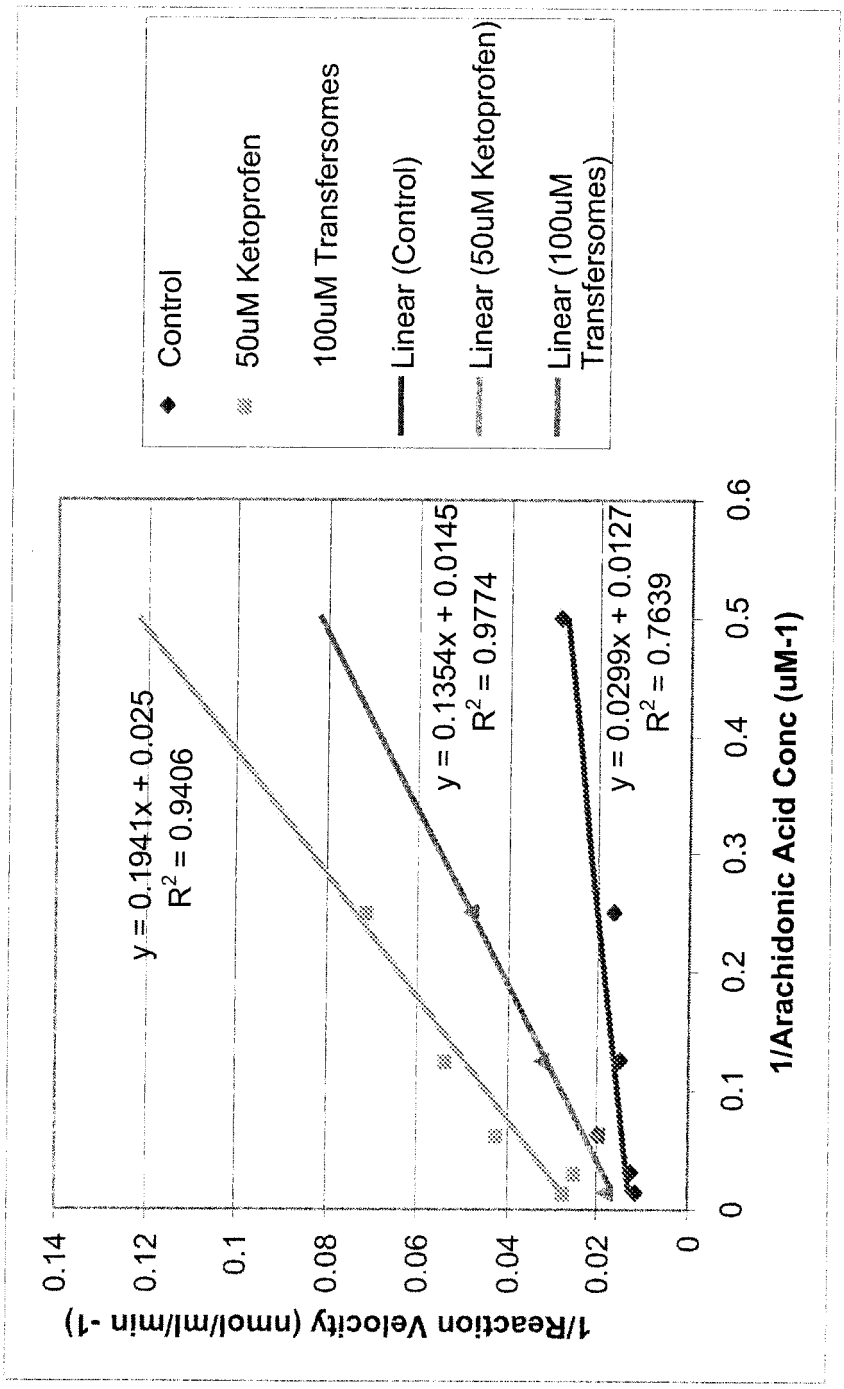

Psoriasis Area and Severity - Erythema
Erythema
2.75
2.50
2.25
2.00
0
1
2
3
Week
Placebo
IDEA-070
p=0.137
p=0.052
p=0.091

Figure 24



	Vmax	Km
0 µM Inhibitor	79	2.4
50 µM Ketoprofen	40	7.8
100 µM Transfersomes	70	9.5

Figure 25

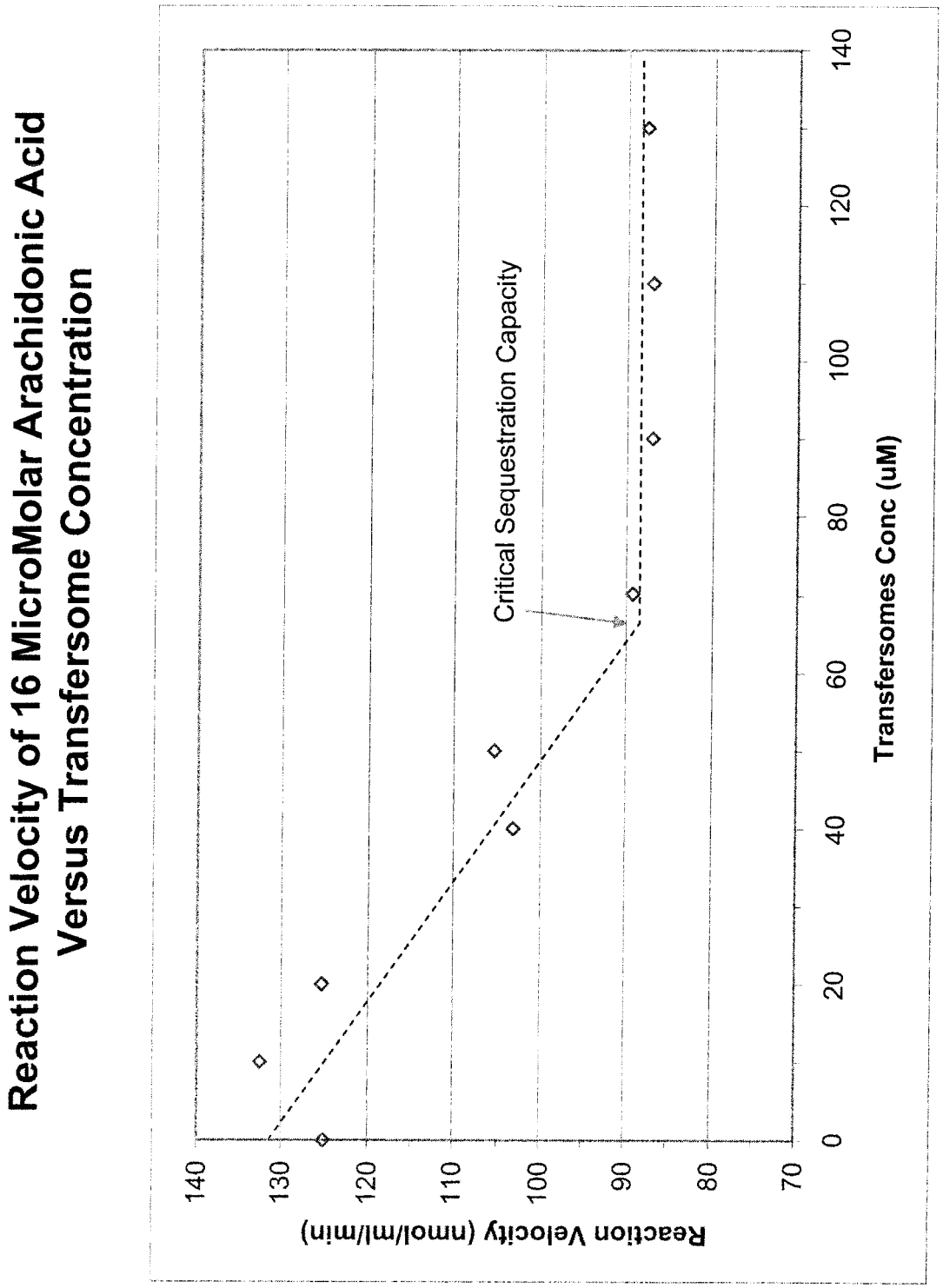

Reaction Velocity of 16 MicroMolar Arachidonic Acid
Versus Transfersome Concentration
Reaction Velocity (nmol/ml/min)
140
130
120
110
100
90
80
70
Transfersomes Conc (uM)
0
20
40
60
80
100
120
140
Critical Sequestration Capacity

Figure 26