

1/29

F1, G1
 5mM Ketor/5mM Phen
 NaPhosphate, pH 7.4
 No Excipients or
 Additives

Related Substance Assay Results for F1, G1 pH7.4

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
Pre Filtered		0.00		
Post Filtered		0.00		
0		0.00		
0.5	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.21
2	0.00	0.00	0.00	2.26
3	0.00	0.00	0.25	1.74
4	0.00	0.00	0.40	2.68
6	0.00	0.21	1.22	5.64
9	0.00	0.00	0.29	8.85
12	2.09	1.36	1.90	16.97

Related Substance Assay Results for F1, G1 pH7.4

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
Pre Filtered		0.09		
Post Filtered		0.00		
0		0.09		
0.5	0.08	0.08	0.00	0.00
1	0.00	0.00	0.00	0.09
2	0.00	0.00	0.00	0.67
3	0.00	0.00	0.00	0.74
4	0.00	0.00	0.23	1.12
6	0.00	0.21	0.66	3.51
9	0.00	0.05	0.36	2.65
12	0.00	0.00	0.64	3.30

FIG. 1

2/29

F1, G2
 5mM Ketor/5mM Phen
 NaPhosphate, pH 7.4
 EDTA

Related Substance Assay Results for F1, G2 pH7.4

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.36
3	0.00	0.00	0.00	1.17
4	0.00	0.00	0.50	1.82
6	0.00	0.00	0.77	2.85
9	0.00	0.00	0.47	2.70
12	0.99	1.01	1.38	5.19

Related Substance Assay Results for F1, G2 pH7.4

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.07		
0.5	0.07	0.00	0.00	0.00
1	0.11	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00
3	0.00	0.00	0.28	0.51
4	0.00	0.00	0.13	1.07
6	0.10	0.00	0.43	3.05
9	0.00	0.00	0.13	1.47
12	0.00	0.00	0.33	1.78

FIG. 2

3/29

F1, G3
5 mM Ketor/5 mM Phen
NaPhosphate, pH 7.4
EDTA + Na metabisulfite

Related Substance Assay Results for F1, G3 pH7.4

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.12	0.29	0.32
1	0.00	0.27	0.46	1.20
2	0.34	0.22	0.44	0.90
3	0.40	0.82	1.77	2.90

Related Substance Assay Results for F1, G3 pH7.4

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.56		
0.5	1.65	1.71	2.74	1.31
1	2.91	3.38	3.84	4.72
2	2.60	2.64	3.22	4.33
3	4.03	4.97	4.76	5.37

FIG. 3

4/29

F2, G1
 5 mM Ketor/5mMPhen
 NaCitrate, pH 6.5
 No Excipients or
 Additives

Related Substance Assay Results for F2 G1 pH6.5

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
Pre Filtered		0.00		
Post Filtered		0.00		
0		0.00		
0.5	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.44
2	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.15
4	0.22	0.00	0.33	0.32
6	0.00	0.00	0.87	3.24
9	0.00	0.00	0.48	1.97
12	0.27	0.00	0.93	5.53

Related Substance Assay Results for F2, G1 pH6.5

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
Pre Filtered		0.00		
Post Filtered		0.05		
0		0.00		
0.5	0.09	0.00	0.00	0.00
1	0.00	0.00	0.00	0.20
2	0.00	0.00	0.00	0.49
3	0.00	0.00	0.00	0.61
4	0.17	0.33	0.00	1.72
6	0.00	0.00	0.41	1.99
9	0.00	0.00	0.18	1.99
12	0.00	0.00	0.25	2.32

FIG. 4

5/29

F2, G2
 5mM Ketor/5 mM Phen
 NaCitrate, pH 6.5
 EDTA

Related Substance Assay Results for F2, G2 pH6.5

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.53
3	0.00	0.00	0.00	0.09
4	0.00	0.00	0.32	1.26
6	0.16	0.16	0.40	1.58
9	0.00	0.00	0.48	1.97
12	0.00	0.00	0.76	2.83

Related Substance Assay Results for F2, G2 pH6.5

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.08		
0.5	0.00	0.17	0.00	0.00
1	0.00	0.00	0.04	0.00
2	0.00	0.00	0.00	0.51
3	0.00	0.00	0.10	0.09
4	0.37	0.23	0.24	0.97
6	0.00	0.00	0.12	1.62
9	0.00	0.00	0.19	0.70
12	0.00	0.00	0.44	0.94

FIG. 5

6/29

F2, G3 5 mM Ketor/5 mM Phen NaCitrate, pH 6.5 EDTA + Na metabisulfite
--

Related Substance Assay Results for F2. G3 pH6.5

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	0.08	0.38
1	0.00	0.00	0.71	0.73
2	0.00	0.18	1.30	1.76

Related Substance Assay Results for F2G3 pH6.5

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.31	0.62	0.60	0.94
1	0.74	1.35	3.02	4.55
2	1.64	1.93	3.97	4.32

FIG. 6

7/29

F3, G1 5 mM Ketor/5 mM Phen NaCitrate, pH 5.5 No Excipients or Additives

Related Substance Assay Results for F3, G1 pH5.5

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
Pre Filtered		0.00		
Post Filtered		0.00		
0		0.00		
0.5	0.00	0.00	0.00	0.65
1	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00
4	0.00	0.00	0.00	0.74
6	0.00	0.00	0.44	1.73
9	0.00	0.00	0.09	0.63
12	0.20	0.00	1.25	4.39

Related Substance Assay Results for F3, G1 pH5.5

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
Pre Filtered		0.00		
Post Filtered		0.00		
0		0.20		
0.5	0.18	0.00	0.00	0.00
1	0.00	0.08	0.00	0.22
2	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.52
4	0.07	0.00	0.50	3.43
6	0.00	0.00	0.47	3.37
9	0.17	0.15	0.33	0.32
12	0.00	0.00	0.98	3.74

FIG. 7

8/29

F3, G2 5 mM Ketor/5 mM Phen NaCitrate, pH 5.5 EDTA
--

Related Substance Assay Results for F3, G2 pH5.5

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.52
3	0.00	0.00	0.00	0.00
4	0.00	0.00	0.00	1.04
6	0.00	0.00	0.13	1.74
9	0.00	0.05	0.35	2.17
12	0.00	0.14	0.45	4.28

Related Substance Assay Results for F3, G2 pH5.5

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.18	0.00	0.00
1	0.21	0.00	0.00	0.15
2	0.00	0.00	0.00	0.30
3	0.00	0.00	0.00	0.00
4	0.16	0.10	0.16	0.75
6	0.00	0.00	0.00	3.45
9	0.00	0.00	0.35	1.42
12	0.00	0.00	0.52	3.59

FIG. 8

9/29

F3, G3
5 mM Ketor/5 mM Phen
NaCitrate, pH 5.5
EDTA + Na metabisulfite

Related Substance Assay Results for F3, G3 pH5.5

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	0.27	0.00
1	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	1.02

Related Substance Assay Results for F3, G3 pH5.5

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.04	0.26	1.03
1	0.12	0.15	0.67	3.44
2	0.00	0.64	2.48	3.59

FIG. 9

10/29

F4, G1 1 mM Ketor/1 mM Phen NaCitrate, pH 4.5 No Excipients or Additives

Related Substance Assay Results for F4, G1 pH4.5

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
Pre Filtered		0.00		
Post Filtered		0.00		
0		0.00		
0.5	0.00	0.00	0.16	0.70
1	0.00	0.00	0.00	1.06
2	0.15	0.13	0.82	3.09

Related Substance Assay Results for F4, G1 pH4.5

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
Pre Filtered		0.18		
Post Filtered		0.09		
0		0.00		
0.5	0.13	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00
2	0.00	0.00	0.11	1.03

FIG. 10

11/29

F4, G2 1 mM Ketor/1 mM Phen NaCitrate, pH 4.5 EDTA

Related Substance Assay Results for F4, G2 pH4.5

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.09	0.00	0.42
1	0.00	0.00	0.00	0.52
2	0.14	0.00	0.68	2.34

Related Substance Assay Results for F4, G2 pH4.5

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.07		
0.5	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.15
2	0.00	0.00	0.00	0.40

FIG. 11

12/29

F4, G3

1 mM Ketor/1 mM Phen
NaCitrate, pH 4.5
EDTA + Na metabisulfite

Related Substance Assay Results for F4, G3 pH4.5

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	0.00	0.00
1	0.00	0.00	0.24	0.17
2	0.00	0.00	0.00	0.89

Related Substance Assay Results for F4, G3 pH4.5

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.19	0.38	0.56	1.12
1	0.15	0.67	1.12	2.52
2	0.88	3.61	5.07	10.08

FIG. 12

13/29

F2, G1

5 mM Ketor/5 mM Phen
NaCitrate, pH 6.5
No Excipients or Additives

F2, G2

5 mM Ketor/5 mM Phen
NaCitrate, pH 6.5
EDTA

Time Point	F2, G1 w/O2 Phenylephrine				F2, G1 w/O2 Ketorolac			
	4° C	25° C	40° C	60° C	4° C	25° C	40° C	60° C
Day 0		0.00				0.00		
Day 14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Day 28	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.12
Day 60	0.00	0.00	0.00	1.46	0.00	0.00	0.06	1.79
Day 90	0.47	0.36	0.25	0.60	0.77	0.64	0.53	0.80
Day 120	0.00	0.00	0.18	3.20	0.11	0.07	0.14	2.18
Day 180	0.00	0.00	0.58	6.38	0.00	0.00	0.25	2.84
Day 270	0.15	0.16	0.63	9.60	0.00	0.00	0.19	3.43
Day 365	2.61	0.70	1.71	15.85	0.00	0.03	0.34	4.17

Time Point	F2, G2 w/O2 Phenylephrine				F2, G2 w/O2 Ketorolac			
	4° C	25° C	40° C	60° C	4° C	25° C	40° C	60° C
Day 0		0.00				0.00		
Day 14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Day 28	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.23
Day 60	0.42	0.23	0.59	1.41	0.15	0.00	0.30	2.33
Day 90	0.33	0.37	0.36	0.62	0.41	0.21	0.27	1.38
Day 120	0.00	0.00	0.77	3.20	0.04	0.04	0.54	3.63
Day 180	0.00	0.13	1.09	4.97	0.00	0.00	0.52	5.52
Day 270	0.00	0.14	2.21	6.55	0.00	0.06	0.59	6.36
Day 365	0.47	2.47	7.61	10.34	0.00	0.16	2.35	6.77

FIG. 13

14/29

F2, G1

5 mM Ketor/5 mM Phen
NaCitrate, pH 6.5
No Excipients or Additives

F2, G2

5 mM Ketor/5 mM Phen
NaCitrate, pH 6.5
EDTA

Time Point	F2, G1 w/N2 Phenylephrine				F2, G1 w/N2 Ketorolac			
	4° C	25° C	40° C	60° C	4° C	25° C	40° C	60° C
Day 0		0.00				0.00		
Day 14	0.00	0.00	0.00	0.00	0.09	0.00	0.00	0.00
Day 28	0.00	0.00	0.00	0.44	0.00	0.00	0.00	0.20
Day 60	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.49
Day 90	0.00	0.00	0.00	0.15	0.00	0.00	0.00	0.61
Day 120	0.22	0.00	0.33	0.32	0.17	0.33	0.00	1.72
Day 180	0.00	0.00	0.87	3.24	0.16	0.16	0.40	1.58
Day 270	0.00	0.00	0.09	4.68	0.00	0.00	0.18	1.99
Day 365	1.13	0.89	2.14	7.10	0.00	0.00	0.27	2.74

Time Point	F2, G2 w/N2 Phenylephrine				F2, G2 w/N2 Ketorolac			
	4° C	25° C	40° C	60° C	4° C	25° C	40° C	60° C
Day 0		0.00				0.10		
Day 14	0.00	0.00	0.00	0.00	0.00	0.22	0.00	0.00
Day 28	0.00	0.00	0.00	0.53	0.00	0.00	0.04	0.00
Day 60	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.51
Day 90	0.00	0.00	0.00	0.09	0.00	0.00	0.10	0.09
Day 120	0.00	0.00	0.32	1.26	0.37	0.23	0.24	0.97
Day 180	0.00	0.00	0.41	1.99	0.13	0.07	0.12	1.62
Day 270	0.00	0.00	0.48	1.97	0.00	0.00	0.19	0.70
Day 365	0.00	0.66	2.29	4.43	0.00	0.00	0.47	0.94

FIG. 14

15/29

F2, G2, A1
 5 mM Ketor/5 mM Phen
 NaCitrate, pH 6.5
 EDTA+Ascorbic acid; no N2
 overlay

Related Substance Assay Results for f5/5_F2, G2, A1

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		1.71		
0.5	6.45	6.20	6.03	12.73
1	5.87	4.30	11.59	15.72

Related Substance Assay Results for f5/5_F2, G2, A1

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.74		
0.5	20.69	27.61	24.13	43.65
1	20.54	23.31	26.53	37.17

FIG. 15

16/29

F2, G2, A2
5 mM Ketor/5 mM Phen
NaCitrate, pH 6.5
EDTA+Cysteine; no N2
overlay

Related Substance Assay Results for f5/5_F2, G2, A2

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	0.57	24.16
1	0.00	0.00	3.85	25.24

Related Substance Assay Results for f5/5_F2, G2, A2

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	9.78	38.77
1	0.00	2.05	20.47	56.81

FIG. 16

17/29

F2, G2, A3
 5 mM Ketor/5 mM Phen
 NaCitrate, pH 6.5
 EDTA+Glutathione; no N2
 overlay

Related Substance Assay Results for f5/5_F2, G2, A3

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	0.08	3.31
1	0.00	0.00	0.71	10.05

Related Substance Assay Results for f5/5_F2, G2, A3

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	1.90	16.08
1	0.72	1.20	8.21	34.62

FIG. 17

18/29

F2, G2, A4
5 mM Ketor/5 mM Phen
NaCitrate, pH 6.5
EDTA+Monothioglycerate; noN2
overlay

Related Substance Assay Results for f5/5_F2, G2, A4

Time (months)	Phenylephrine % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.00	1.72	9.50
1	0.00	0.51	2.76	5.77

Related Substance Assay Results for f5/5_F2, G2, A4

Time (months)	Ketorolac % Related Substances			
	2-8° C	25° C	40° C	60° C
0		0.00		
0.5	0.00	0.42	10.84	29.94
1	0.31	10.23	20.00	29.06

FIG. 18

19/29

450 mM PE
NaCitrate, pH 6.5
No Excipients or Additives

Related Substance Assay Results for PE-f450; Lot 1050193

Time (months)	Phenylephrine Related Substances				Total Related Substances			
	4° C	25° C	30°C	40°C	4° C	25° C	30°C	40°C
0		0.00				0.00		
0.5								
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.01
4	0.01	0.00	0.00	0.06	0.01	0.00	0.00	0.06

FIG. 19

20/29

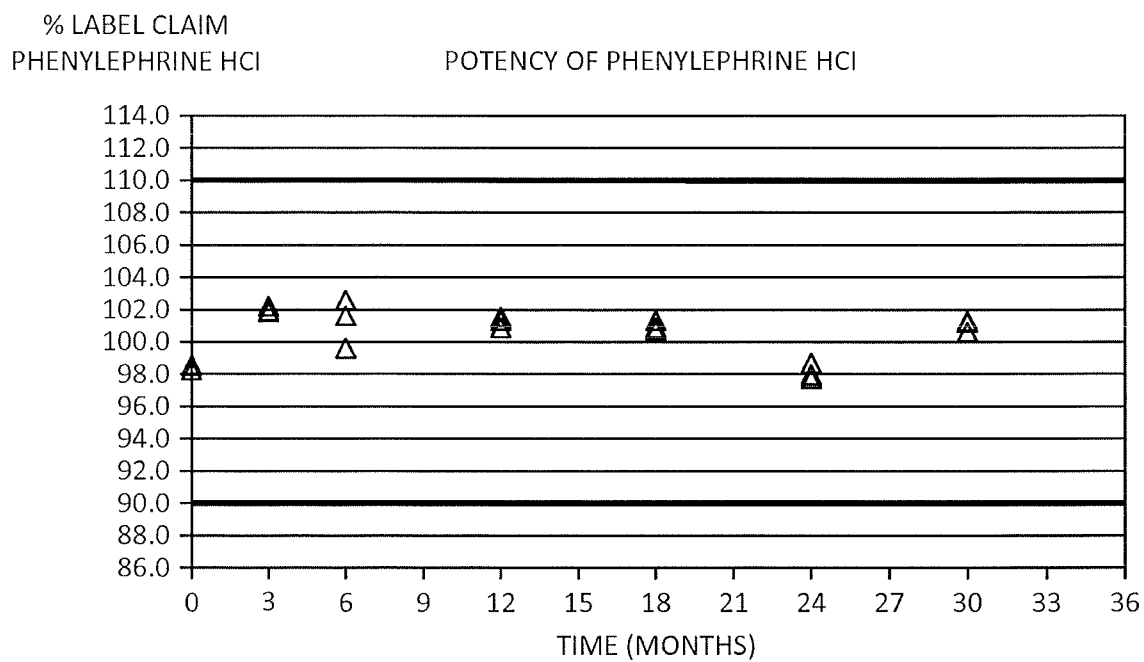


FIG. 20A

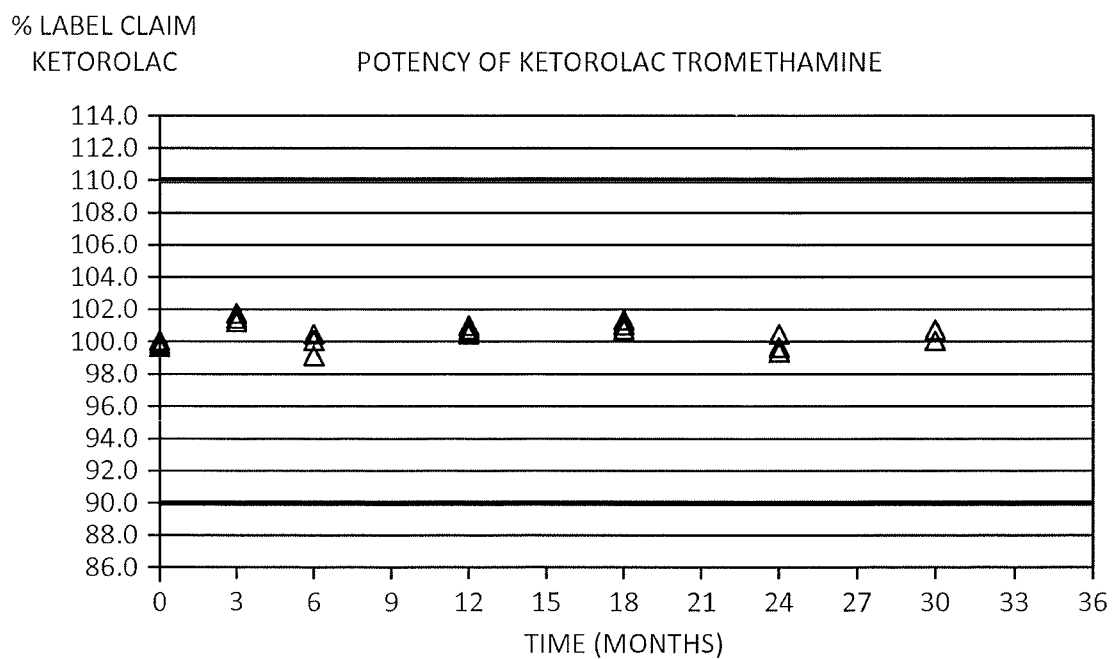
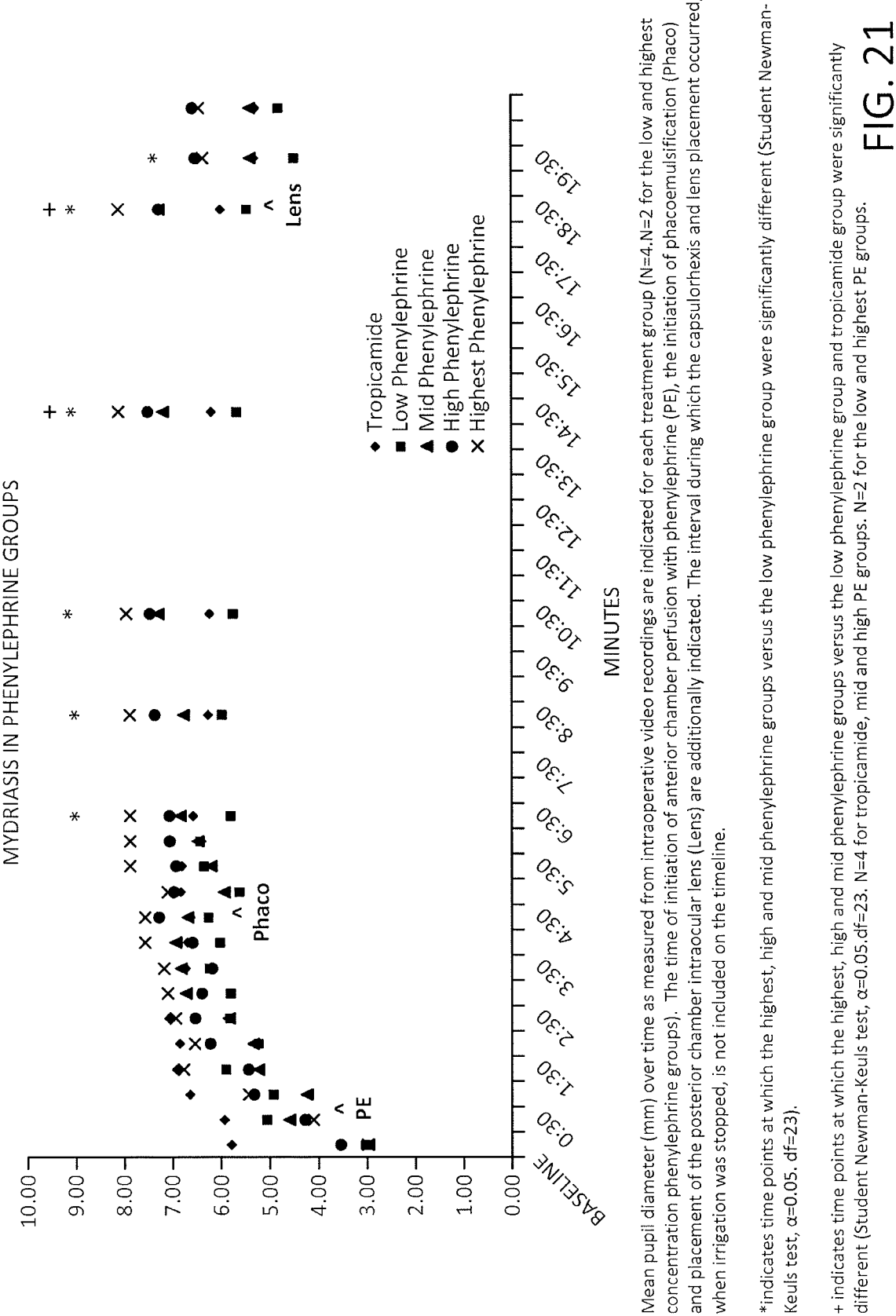
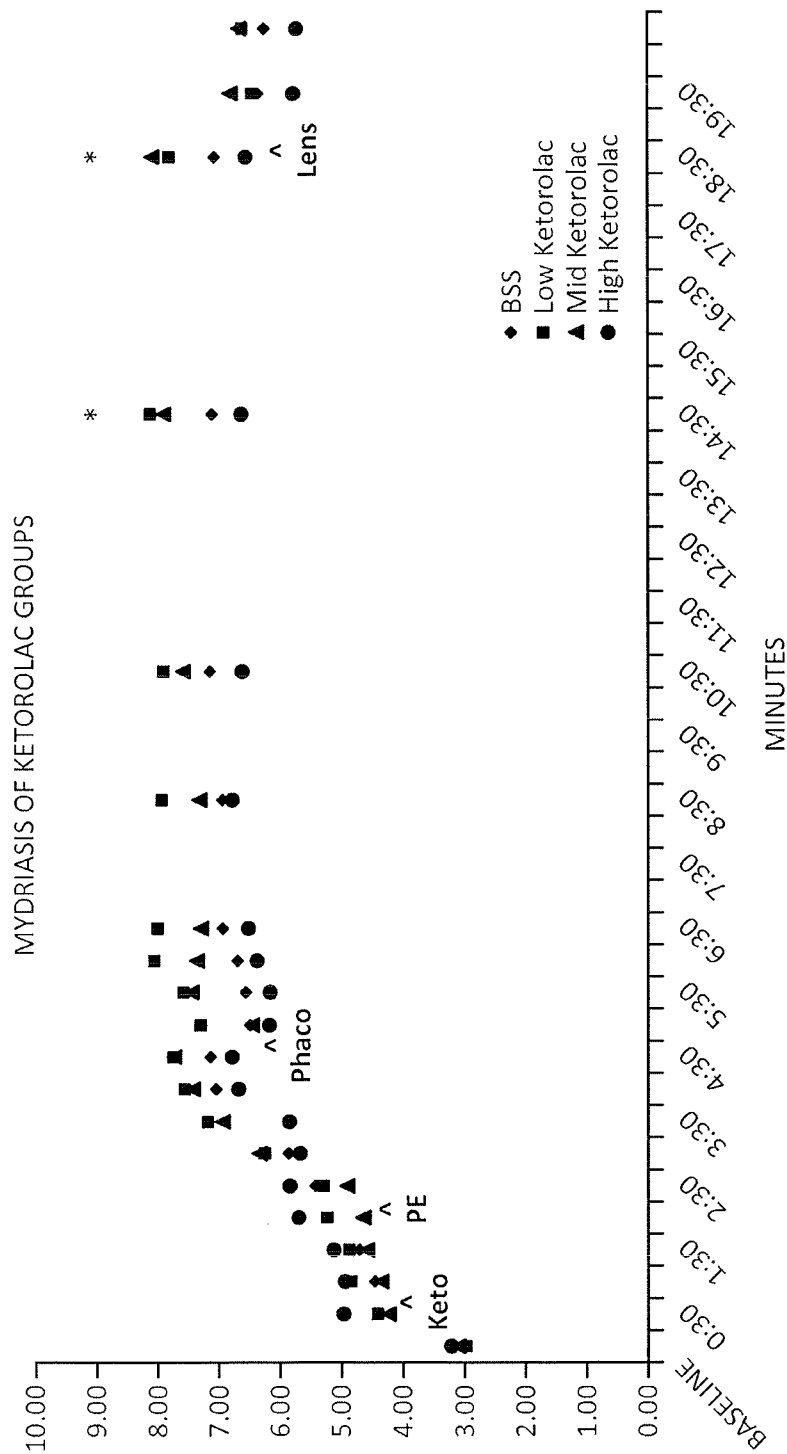


FIG. 20B

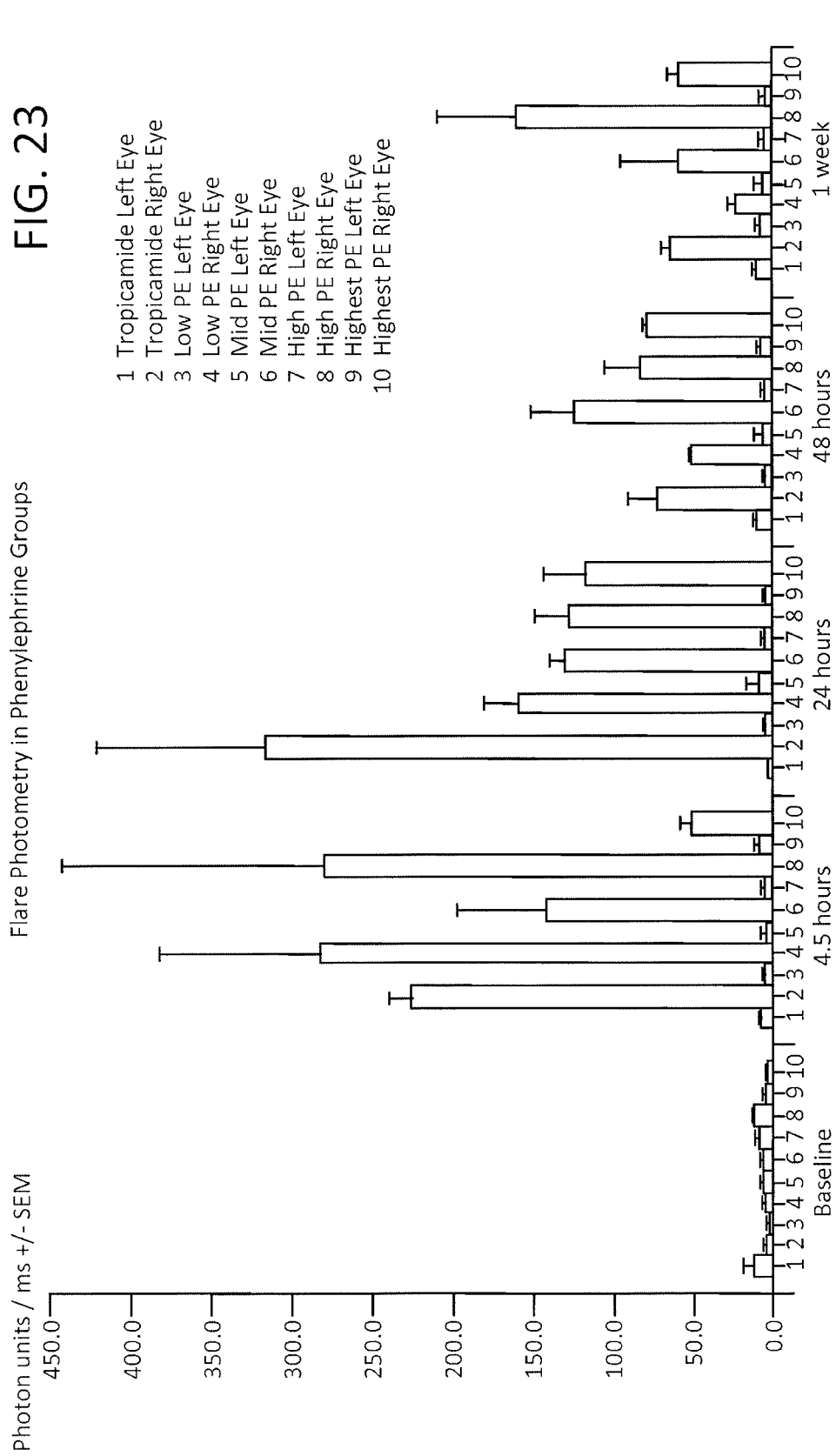




Mean pupil diameter (mm) over time as measured from intraoperative video recordings are indicated for each treatment group (N=4). The time of initiation of anterior chamber perfusion with phenylephrine (PE), the initiation of phacoemulsification (Phaco) and placement of the posterior chamber intraocular lens (Lens) are additionally indicated. The interval during which the capsulorhexis and lens placement occurred, when irrigation was stopped, is not included on the timeline.

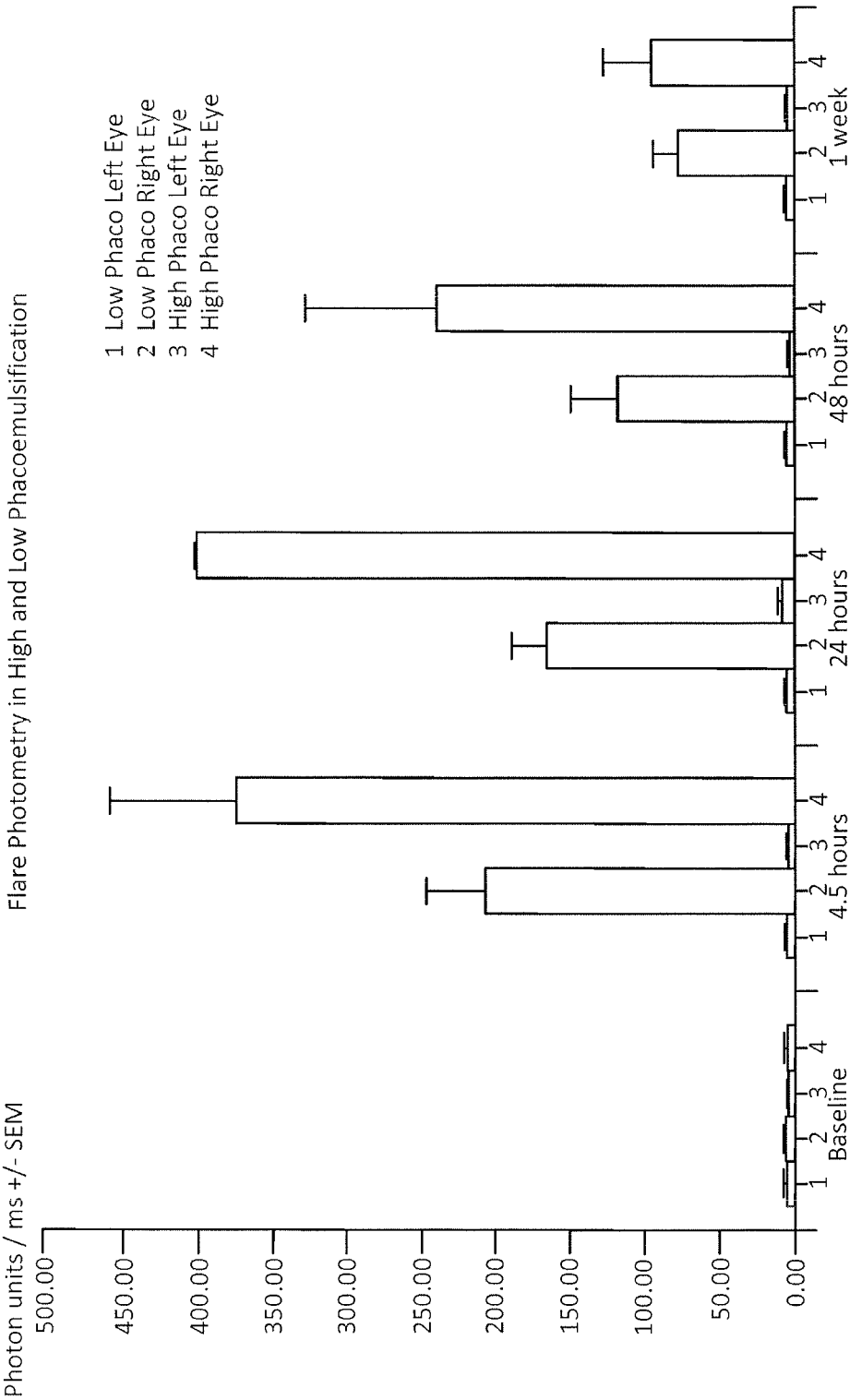
* indicates time points at which the low and mid concentration ketorolac group versus the BSS and high concentration ketorolac group versus the BSS and high concentration ketorolac group were significantly different (Student Newman-Keuls test, $\alpha=0.05=0.05$, $df=23$). N=4 per group.

FIG. 22



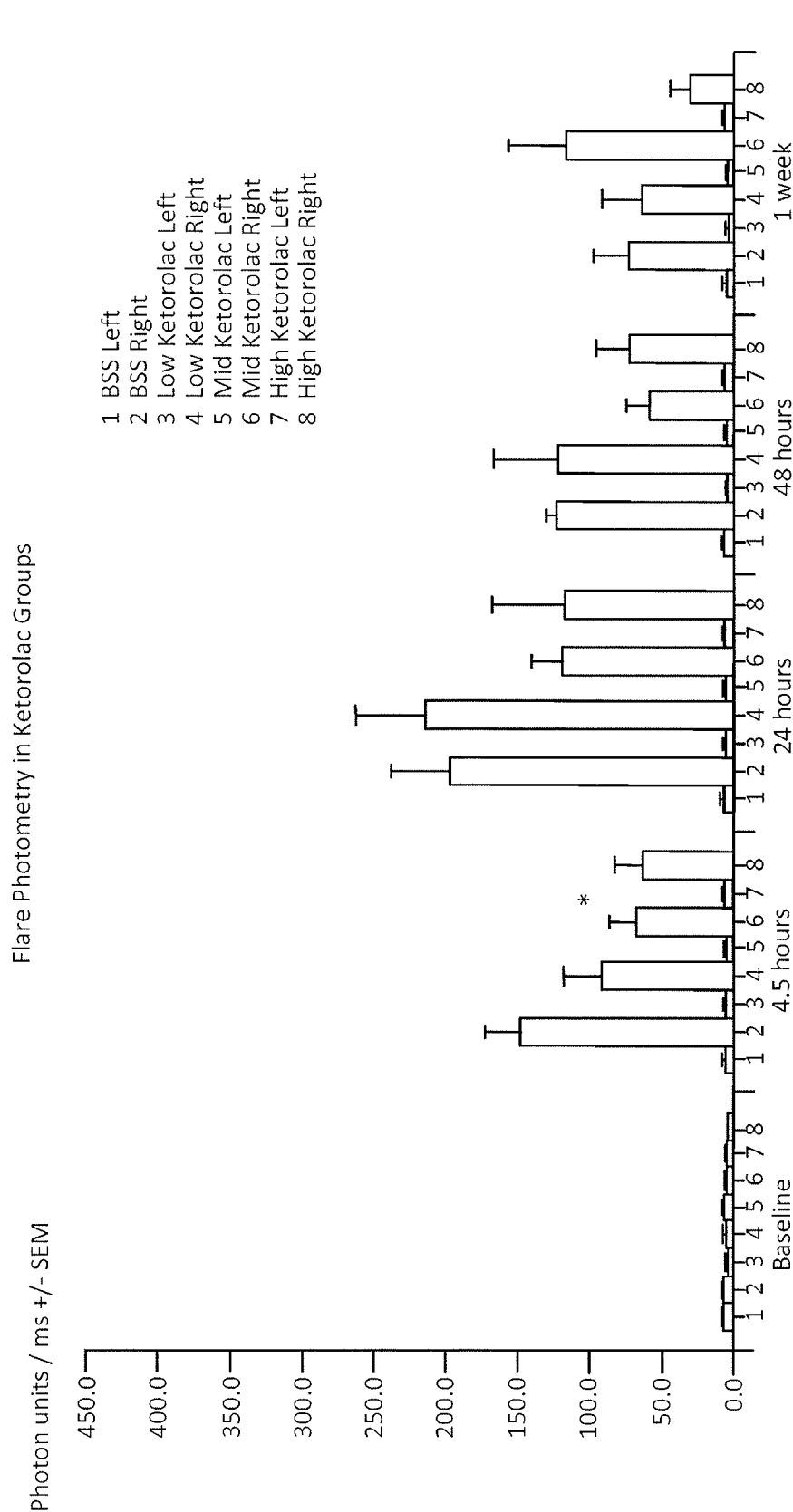
Mean flare measures +/- the standard error for the control and treated eye in the phenylephrine treatment group. Means excluded the four eyes in the tropicamide control and high phenylephrine groups which received longer duration phacoemulsification (>45 secs). There was a significant effect of time on flare measures in all treatment groups ($F=17.14$, $p<0.0001$), reflecting the inflammatory response to the surgical intervention, but no significant difference between treatment groups when including or excluding the long duration phacoemulsification eyes. $N=4$ for tropicamide, mid and high PE groups. $N=2$ for the low and highest PE groups.

24/29



Mean flare measures +/- the standard error for the phenylephrine and tropicamide treated eyes in the Phase 1 study that received either low phacoemulsification energy (<25 secs) or high phacoemulsification energy (>45 secs). Differences were significant evaluating across all time points (F=4.42, p<0.0018; Student Newman-Keuls test, $\alpha=0.05$, df=14; N=12 for the low phaco and 4 for the high phaco groups), indicating a correlation between phacoemulsification duration and flare photometer measures.

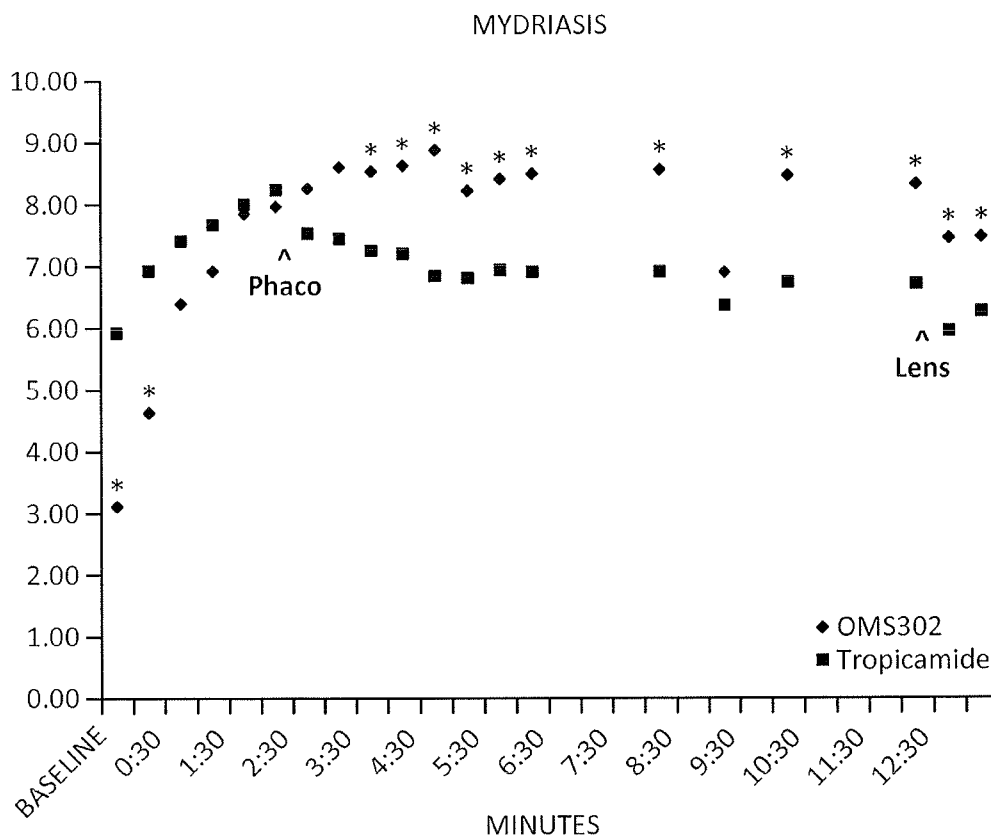
FIG. 24



Mean flare measures +/- the standard error for the control and treated eye in the ketorolac treatment group.
* The combined and high concentration ketorolac groups were significantly different from the BSS control group at the 4.5 hour time point (F=5.17, P<0.0223; Student Newman-Keuls test, $\alpha=0.05$, df=13; N=4 per group). The study was not sufficiently powered to reveal significance at any other time point.

FIG. 25

26/29



Mean pupil diameter (mm) over time as measured from intraoperative video recordings are indicated for each treatment group (N=7 per group). The time of initiation of phacoemulsification (Phaco) and placement of the posterior chamber intraocular lens (Lens) are additionally indicated. The interval during which the capsulorhexis and lens placement occurred, when irrigation was stopped, is not included on the timeline.

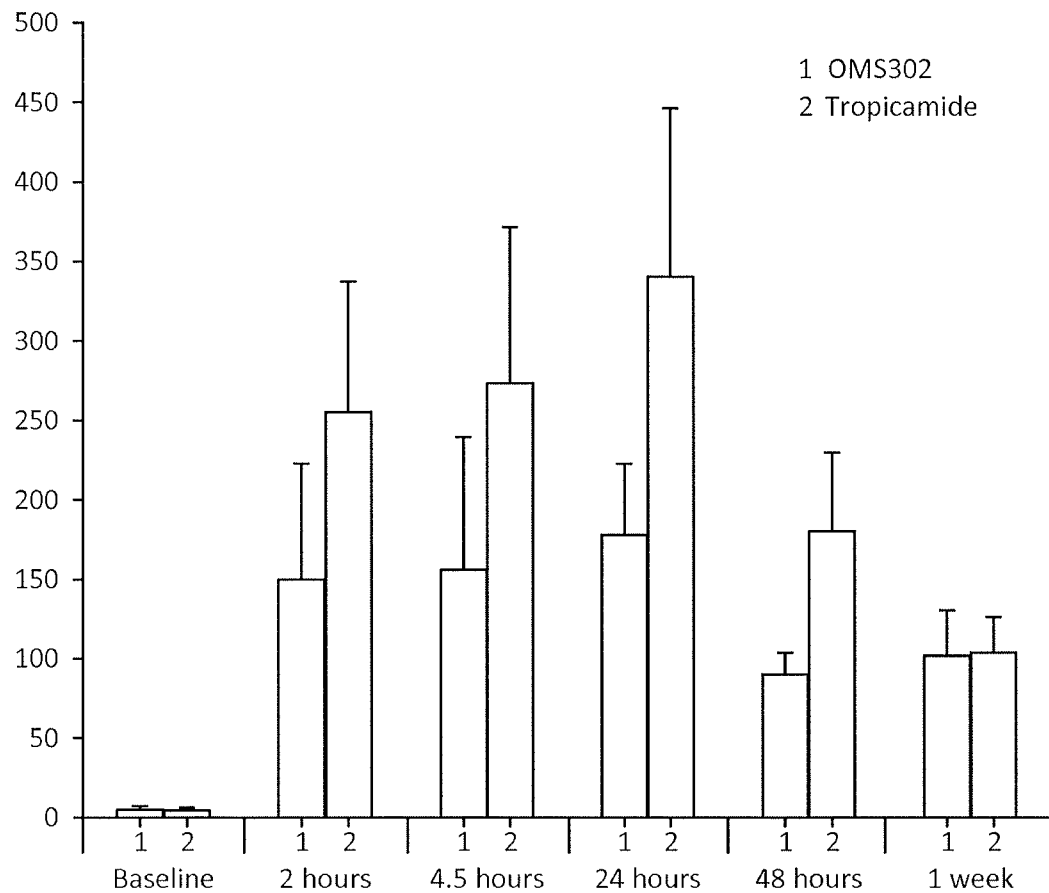
*indicates time points at which the PE-KE (OMS302) versus the tropicamide control group were significantly different (Student Newman-Keuls test, $\alpha=0.05$, $df=12$).

FIG. 26

27/29

FLARE PHOTOMETRY

Photons units /ms +/- SEM



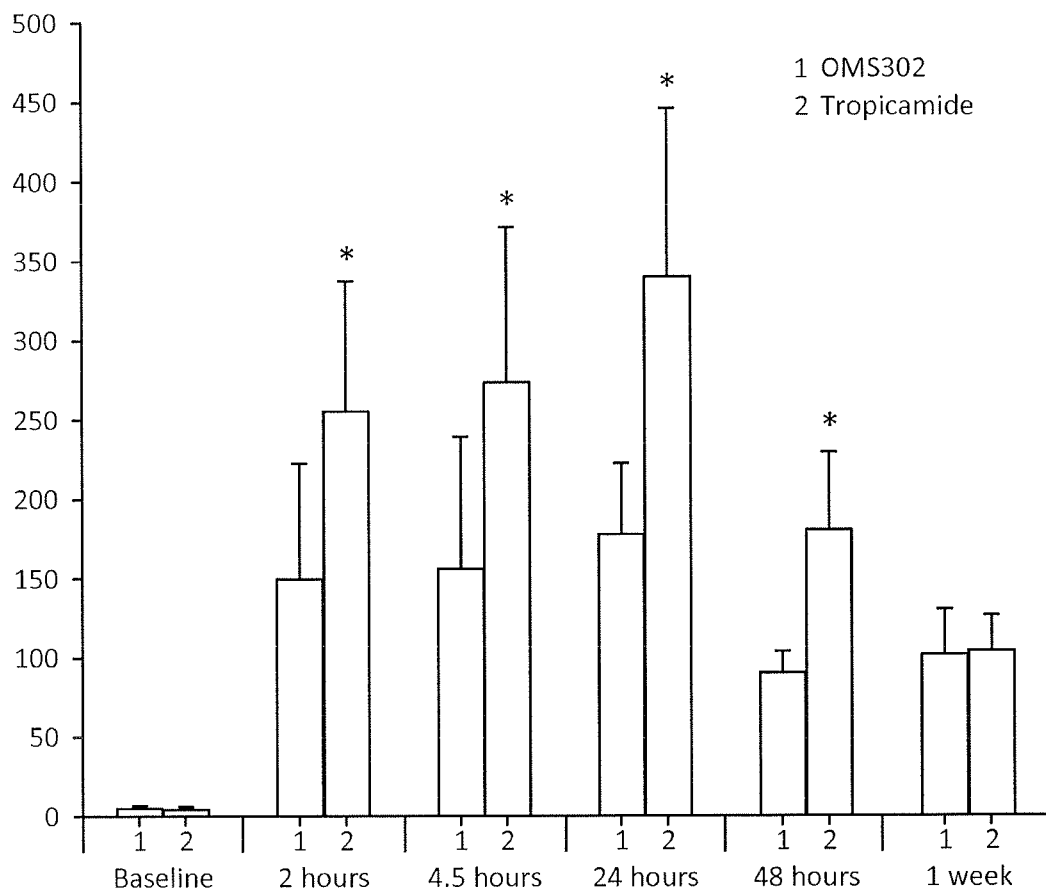
Mean flare measures +/- the standard error for the operative eye in the PE-KE (OMS302) and tropicamide control treatment groups. There was a significant effect of time on flare measures in both treatment groups ($F=4.94$, $p<0.0008$), reflecting the inflammatory response to the surgical intervention, but no significant difference between treatment groups at any time point when including all subjects ($F=3.32$, $P<0.0935$; Student Newman-Keuls test, $\alpha=0.05$, $df=12$).

FIG. 27

28/29

FLARE PHOTOMETRY WITHOUT EXCLUDED SUBJECT

Photons units /ms +/- SEM



Mean flare measures +/- the standard error for the operative eye in the PE-KE (OMS302) and tropicamide control treatment groups with the exclusion of subject X932, which exhibited limited phenylephrine induced dilation. There was a significant difference between treatment groups at 2, 4.5, 24 and 48 hours, indicated by * ($F=3.32$, $P<0.0935$ check stats p value; Student Newman-Keuls test $\alpha=0.05$, $df=12$).

FIG. 28

29/29

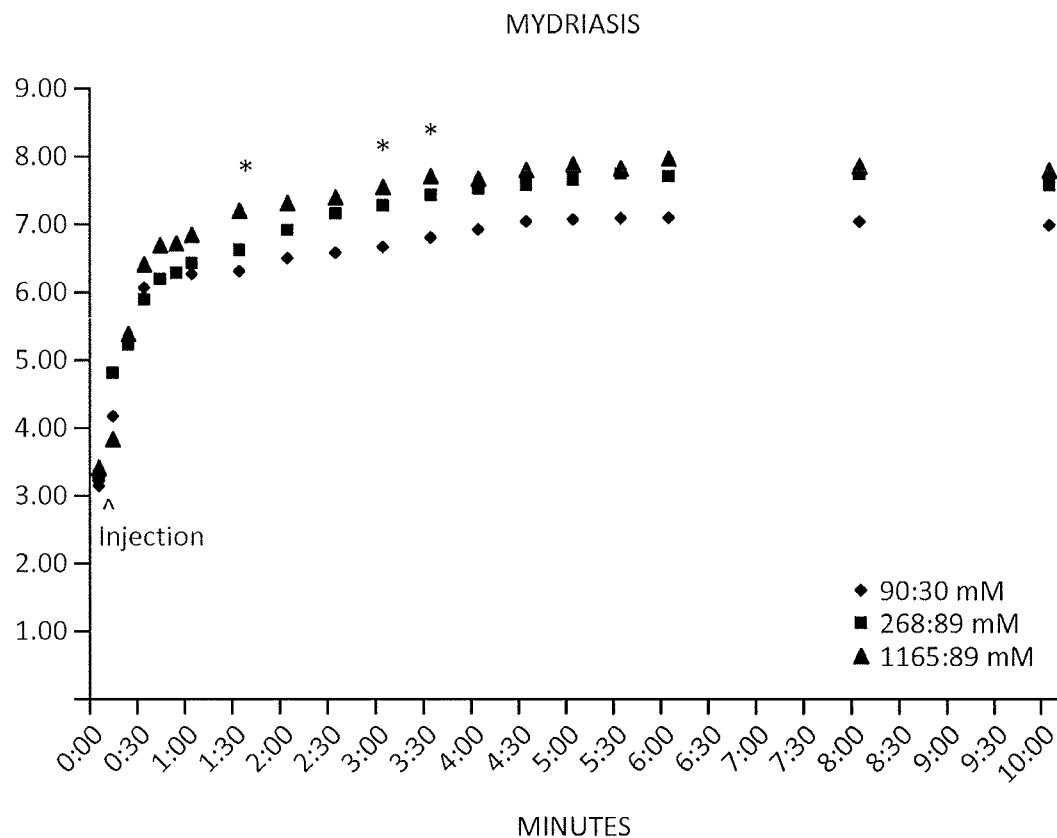


FIG. 29