

Difluprednate Ophthalmic Emulsion, 0.05%: Safety and Efficacy Review

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Sirion Therapeutics Inc.
Presentation to the
Dermatologic and Ophthalmic Drugs Advisory
Committee Meeting
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Sirion Presentation

- Program objectives
- Difluprednate background
- Sirion clinical development plan
- Sirion Phase 3 studies
 - Efficacy
 - Safety
- Conclusions

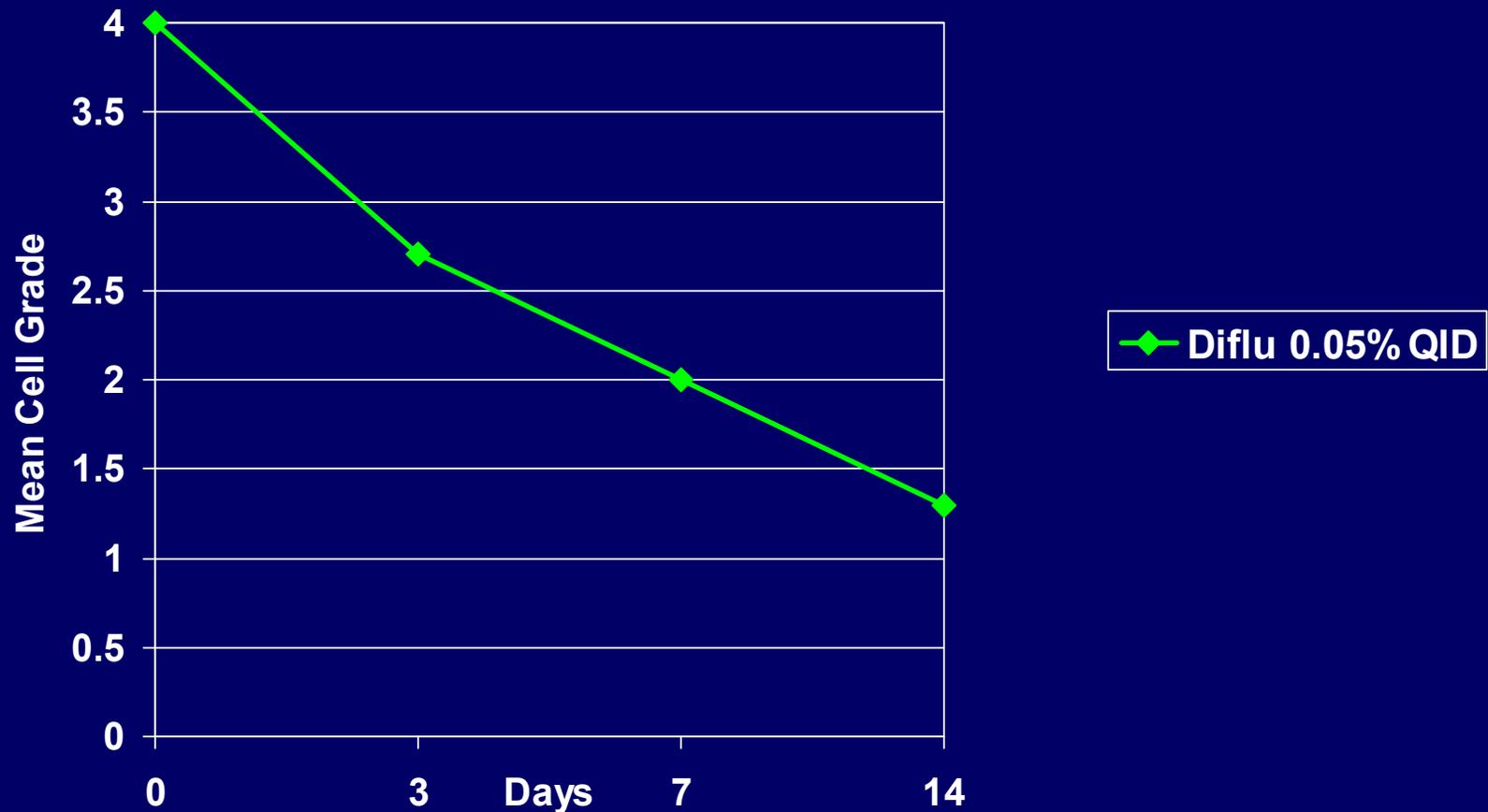
Sirion Clinical Program Objectives

- Demonstrate that difluprednate ophthalmic emulsion 0.05% is safe and effective for the treatment of inflammation and pain following ocular surgery
- Select a dosing schedule based on the benefit to risk profile

Difluprednate Background

- Novel synthetic prednisolone derivative
- Discovered in 1970
- New chemical entity for ophthalmology in USA
- Classified as a very strong steroid (Hino,2001; Furue, 2005)
- Marketed in Japan as topical dermatological formulation since 1979
- Licensed from Senju Pharmaceuticals based on demonstrated efficacy in uveitis

Senju Open Label Refractory Uveitis Study: Mean AC Cell Grade



- 72% of subjects experienced a reduction in AC Cell Grade to ≤ 1 by Day 14

Potency of Topical Glucocorticoids

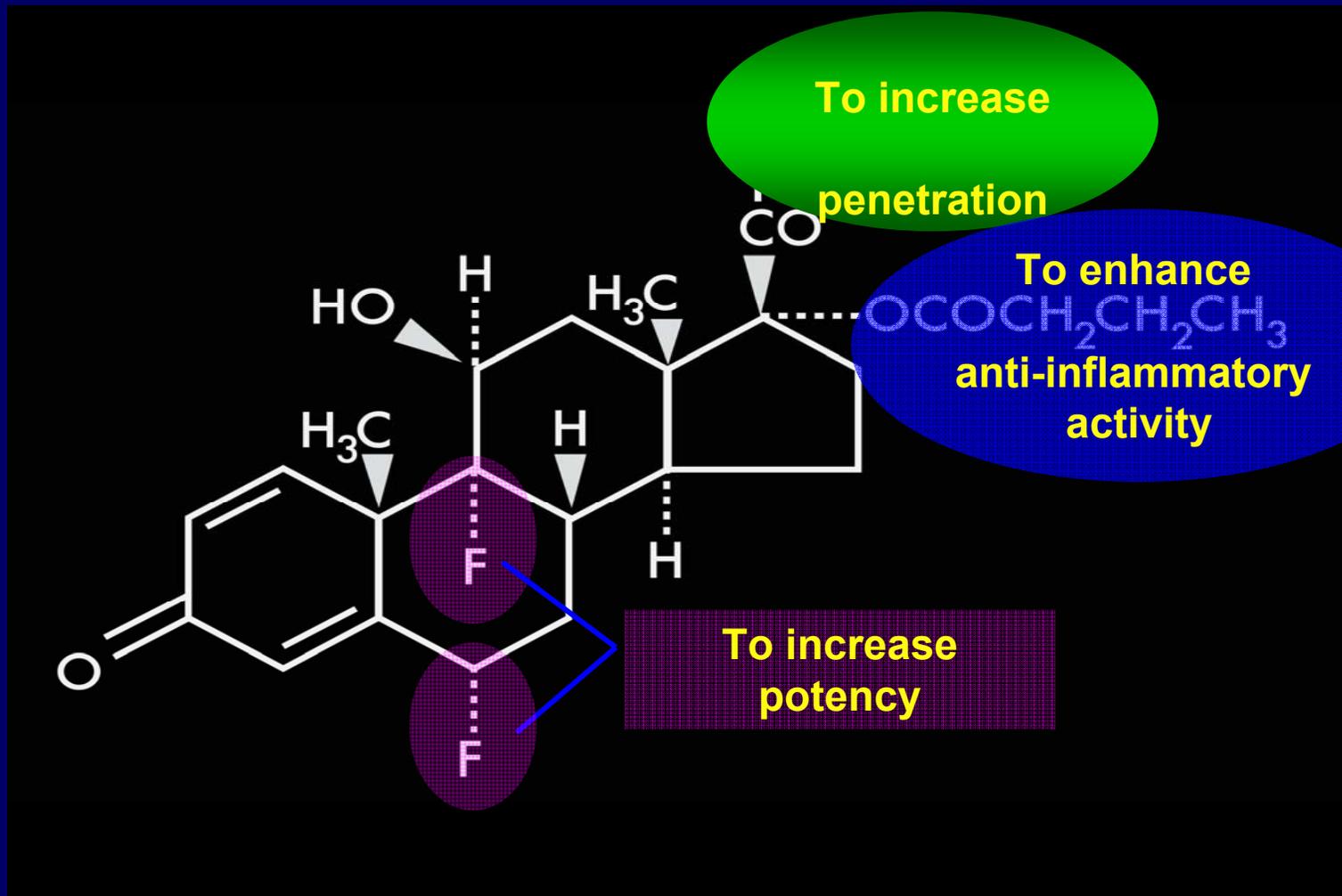
Name	Glucocorticoid Potency	Half-life (T _{1/2} in hours)
Hydrocortisone	1	8 – 12
Prednisone	3.5	18 – 36
Prednisolone	4.0	16 – 36
Methylprednisolone	5.0	18 – 36
Triamcinolone	5.0	12 – 36
Betamethasone	25	36 – 54

All potencies relative to hydrocortisone, which is assigned a value of 1

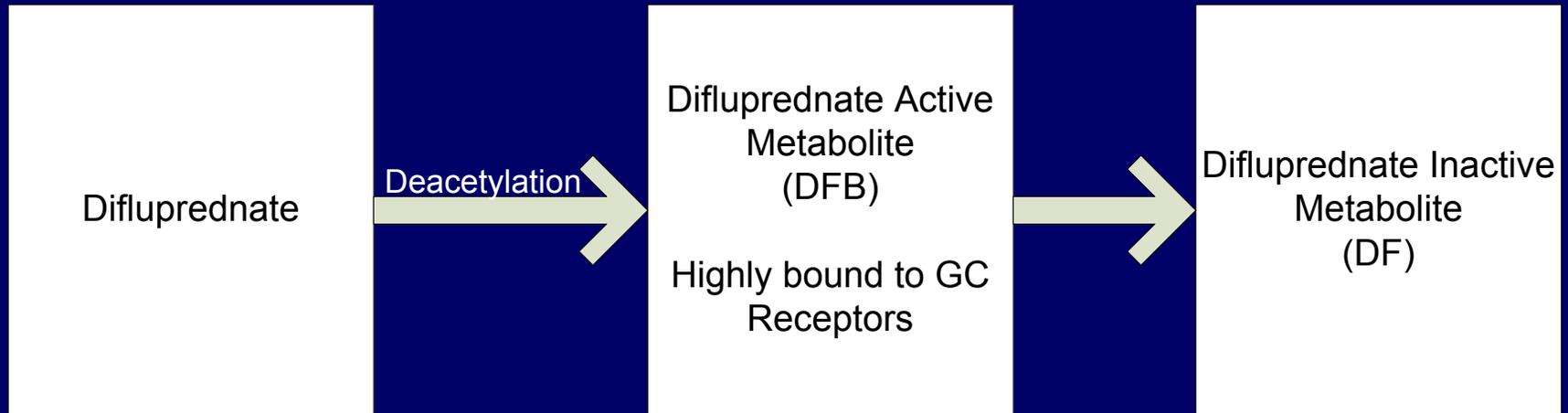
Difluprednate Molecule

- Designed to penetrate epithelium and rapidly act upon glucocorticosteroid receptors
- Modifications were made to the prednisolone structure
 - C6- and C9-positions fluorinated
 - ✓ To add to the potency
 - Acetic acid at C21
 - ✓ To increase lipophilicity and penetration
 - Butyric acid at C17
 - ✓ To enhance anti-inflammatory activity

Structural Modifications



Difluprednate Metabolism



Difluprednate Glucocorticoid Receptor Binding

Studies in rabbits:

- 0.05% > 0.01% and 0.002%
- T_{max} in anterior chamber 30 – 60 mins
- T_{max} 50% of that for betamethasone 0.1%;
- Iris/ciliary body GC receptor binding:
 - difluprednate 0.05% significantly > betamethasone
 - constant up to 120 minutes
 - duration of activity 2x betamethasone

Preclinical data summary

- High potency in receptor binding— lower dose
- Long half life supports less frequent dosing
- Metabolism in tissue results in lower systemic steroid exposure

Difluprednate Phase 3 Studies

Sirion, US:

- Two placebo-controlled Phase 3 studies -
Postsurgical inflammation and pain

Senju, Japan:

- Three active-controlled Phase 3 studies -
 - Postsurgical inflammation (2)
 - Uveitis (1)

Difluprednate: Safety Studies

Seven clinical studies provide safety data

Phase 3

- 2 - postsurgical inflammation, Sirion
- 1 - postsurgical inflammation, Senju
- 1 - uveitis, Senju
- 1 - open label, severe uveitis, Senju

Phase 2

- 1 - postsurgical inflammation, Senju
- 1 - uveitis, Senju

Sirion Phase 3: Clinical Development Plan

- 2 replicative studies in postsurgical inflammation
- QID and BID difluprednate vs placebo (vehicle)
- Safety and efficacy

Sirion Phase 3

- *Dose selection rationale*
- Study design
- Inclusion/exclusion criteria
- Demographics and baseline characteristics
- Efficacy results
- Safety results
- Summary and conclusions

Dose Selection Rationale: Preclinical

- 0.05% is the maximum concentration that can be formulated in an emulsion
- Emulsion formulation demonstrated 4x higher penetration than suspension
- Rabbit GC receptor binding activity
 - One drop difluprednate, 0.002%, 0.01%, and 0.05% compared with one drop betamethasone 0.1%
 - Difluprednate 0.05% → stronger GC receptor binding activity than betamethasone 0.1%
- Rabbit postsurgical acute inflammation model
 - Difluprednate 0.05%, was superior to 0.002%, 0.01%, betamethasone 0.1% or saline

Dose Selection Rationale: Clinical

3 clinical studies conducted to evaluate optimum dose

- Phase 1: difluprednate at 0.002%, 0.01%, 0.05%, and placebo
 - Single instillation of 2 drops in the study eye (N=6/treatment group; N=18 placebo)
- Phase 1: difluprednate at 0.01%, 0.05%, and placebo
 - 7 day instillation of 2 drops QID in the study eye (N=6/treatment group; N=12 placebo)

Phase 1 Results: Difluprednate 0.05% was well tolerated

- Phase 2: Postsurgical inflammation; difluprednate, 0.002% vs. 0.05%
 - 7 day instillation of 1 drop QID in the study eye (N=6; N=4 in 0.05%)

Phase 2 Results: Difluprednate, 0.05% was well tolerated and more efficacious for the treatment of postsurgical inflammation

Sirion Phase 3

- Dose selection rationale
- *Study design*
- Inclusion/exclusion criteria
- Demographics and baseline characteristics
- Efficacy results
- Safety results
- Summary and conclusions

Clinical Development Recommendations From FDA Implemented by Sirion

- Changed primary endpoint from Day 15 to Day 8
- Changed Flare Grade 0 to exclude trace
- Anterior Chamber Cell Grading:

Original Sirion grading scale: Grade 0 < 5 cells
Recommended by FDA Grade 0 = 0 cells

- Grading scale used in Sirion Phase III studies:

Grade 0 ≤ 1 cells

Grade 1 2 - 10 cells

Grade 2 11 - 20 cells

Grade 3 21 - 50 cells

Grade 4 >50 cells

Rationale for Cell Grade $0 \leq 1$ Cell

Substantial evidence exists that normal eyes have at least 1 cell
(Guillen-Monterrubio et al, 1997; Shah, 1991; Yang, 2004)

- Guillen-Monterrubio - 263 eyes of 141 healthy normal subjects aged 12 – 89 yrs

- Mean cell count of 1.1

- Cell counts highest in 50-59 yr old; mean count of 2.2 (range of 0 – 18.1)

- Shah - 106 eyes in 53 healthy subjects; 10.4% had 1 cell

- Yang - 52 eyes in 52 healthy subjects; mean cell count of 0.9 (range of 0 – 2.0)

Rationale for Cell Grade $0 \leq 1$ Cell

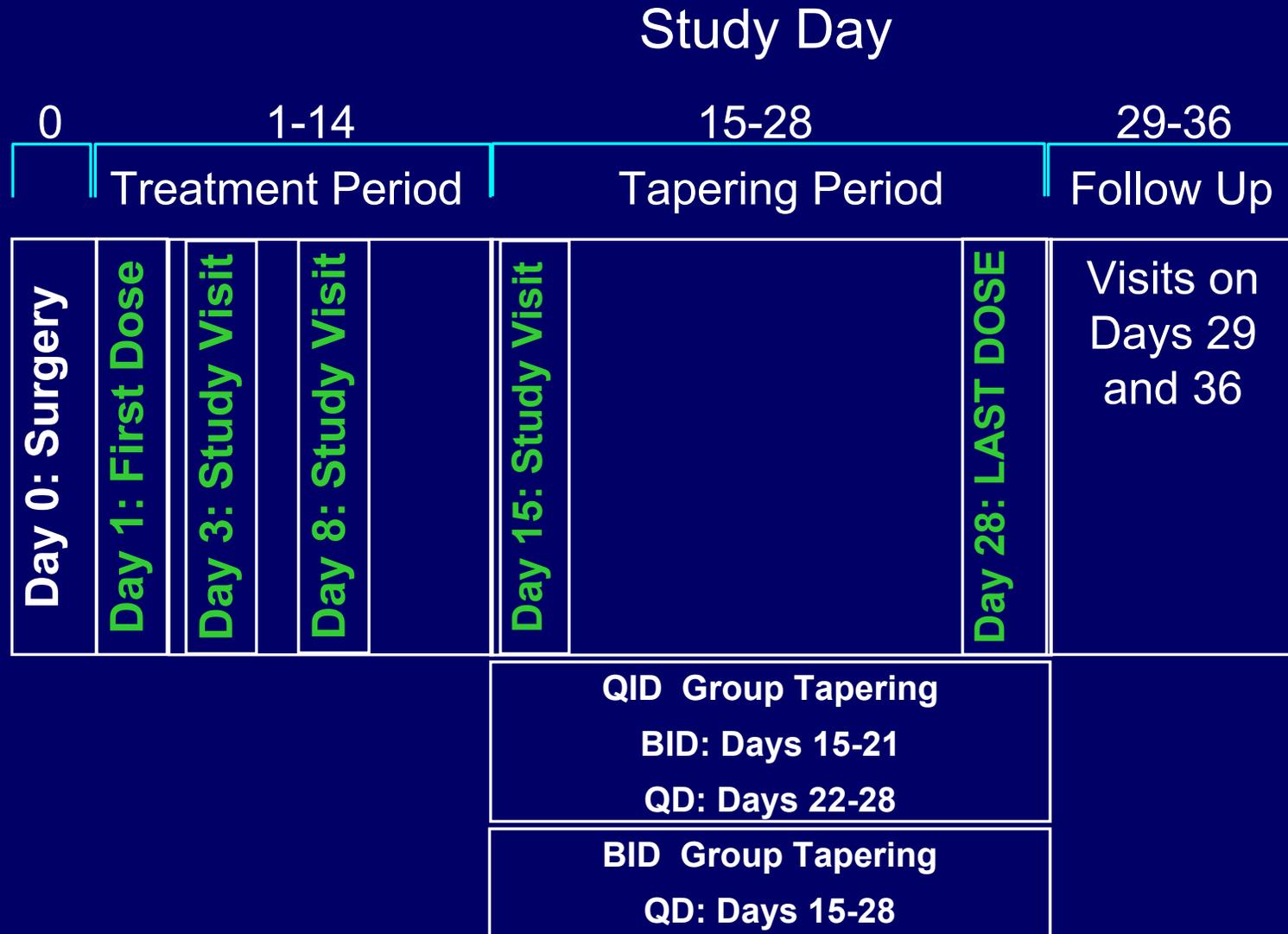
- 3 published clinical trials of rimexolone used this definition (Biswas et al, 2004; Foster et al, 1996)
- 2 trials of loteprednol used a definition of Grade $0 \leq 4$ cells and Grade $0 \leq 5$ cells (Loteprednol Etabonate US Uveitis Study Group: *Am. J. Ophthalmol* 1999 May; 127(5):537-44)
- Mydriatic agents were permitted concomitant meds and these can release cells and pigment granules and affect cell measurements

Sirion Phase 3: Study Design

- 2 multicenter, randomized, double-masked, placebo-controlled
- 24/26 centers in the US enrolled
- 1 drop administered BID or QID for 14 days
 - Followed by 14 days of tapering

Difluprednate Ophthalmic Emulsion 0.05% BID N=111	Difluprednate Ophthalmic Emulsion 0.05% QID N=107	Placebo (Vehicle) BID or QID N=220
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Sirion Phase 3: Study Design



Sirion Phase 3

- Dose selection rationale
- Study design
- *Inclusion/exclusion criteria*
- Demographics and baseline characteristics
- Efficacy results
- Safety results
- Summary and conclusions

Sirion Phase 3: Key Inclusion Criteria

- Unilateral ocular surgery on the day prior to study enrollment
- Anterior chamber cell grade ≥ 2 on the day after surgery (Day 1)

Sirion Phase 3: Key Presurgical Exclusion Criteria

- Use of systemic/ocular corticosteroids or NSAIDs
- Glaucoma or ocular hypertension
- History of steroid-related IOP increase
- Endogenous uveitis
- Corneal abrasion or ulceration
- Active viral, bacterial, or fungal infection
- Planned surgery on the contralateral eye
- Use of contact lenses during the study

Sirion Phase 3: Key Exclusion Criteria 24 Hrs Postsurgery (Day 1)

- IOP \geq 24 mm Hg
- Anterior chamber cell count $<$ grade 2
- Intraoperative complications
 - Hemorrhage, intravitreal gas, etc.

Sirion Phase 3

- Dose selection rationale
- Study design
- Inclusion/exclusion criteria
- *Demographics and baseline characteristics*
- Efficacy results
- Safety results
- Summary and conclusions

Sirion Phase 3: Demographics and Baseline Characteristics (QID vs Placebo)

	QID		Placebo	
	Study 1	Study 2	Study 1	Study 2
	(N=55)	(N=52)	(N=107)	(N=113)
Age (mean yrs)	68	68	69	70
(range)	(39-86)	(24-87)	(32-96)	(41-88)
Females	56%	56%	48%	62%
IOP (mm Hg)	16.7	14.3	15.8	14.8
Irides (dark)	75%	38%	63%	47%

Sirion Phase 3: Demographics and Baseline Characteristics (BID vs Placebo)

	BID		Placebo	
	Study 1 (N=57)	Study 2 (N=54)	Study 1 (N=107)	Study 2 (N=113)
Age (mean yrs) (range)	71 (29-87)	71 (49-88)	69 (32-96)	70 (41-88)
Females	53%	56%	48%	62%
IOP (mm Hg)	17.2	14.3	15.8	14.8
Irides (dark)	53%	46%	63%	47%

Sirion Phase 3: Demographics and Baseline Characteristics (QID vs Placebo)

	QID		Placebo	
	Study 1 (N=55)	Study 2 (N=52)	Study 1 (N=107)	Study 2 (N=113)
Caucasian	87.3%	90.4%	89.7%	88.5%
African-American	12.7%	7.7%	7.5%	5.3%
Asian	0.0%	0.0%	1.9%	1.8%
Other	0.0%	1.9%	0.9%	4.4%
Hispanic/Latino	21.8%	1.9%	26.2%	1.8%

Sirion Phase 3: Demographics and Baseline Characteristics (BID vs Placebo)

	BID		Placebo	
	Study 1 (N=57)	Study 2 (N=54)	Study 1 (N=107)	Study 2 (N=113)
Caucasian	80.7%	79.6%	89.7%	88.5%
African-American	15.8%	13.0%	7.5%	5.3%
Asian	1.8%	1.9%	1.9%	1.8%
Other	1.8%	5.5%	0.9%	4.4%
Hispanic/Latino	17.5%	0.0%	26.2%	1.8%

Sirion Phase 3

- Dose selection rationale
- Study design
- Inclusion/exclusion criteria
- Demographics and baseline characteristics
- *Efficacy results*
- Safety results
- Summary and conclusions

Sirion Phase 3: Efficacy Results (ITT–LOCF)

Proportion of subjects with:

- AC cell grade of “0”
 - Days 3, 8, and 15
 - QID vs placebo
 - BID vs placebo

- Pain score = 0
 - Days 3, 8, and 15
 - QID vs placebo
 - BID vs placebo

Sirion Phase 3: AC Cell Grade = “0” QID vs Placebo

	QID	Placebo	P value
Study 1	N=55	N=105	
Day 3	9.3%	1.9%	<i>P</i> = 0.0540
Day 8	34.5%	12.4%	<i>P</i> = 0.0014
Day 15	65.5%	17.1%	<i>P</i> < 0.0001
Study 2	N=52	N=113	
Day 3	3.8%	1.8%	<i>P</i> = 0.4093
Day 8	34.6%	6.2%	<i>P</i> < 0.0001
Day 15	59.6%	15.0%	<i>P</i> < 0.0001

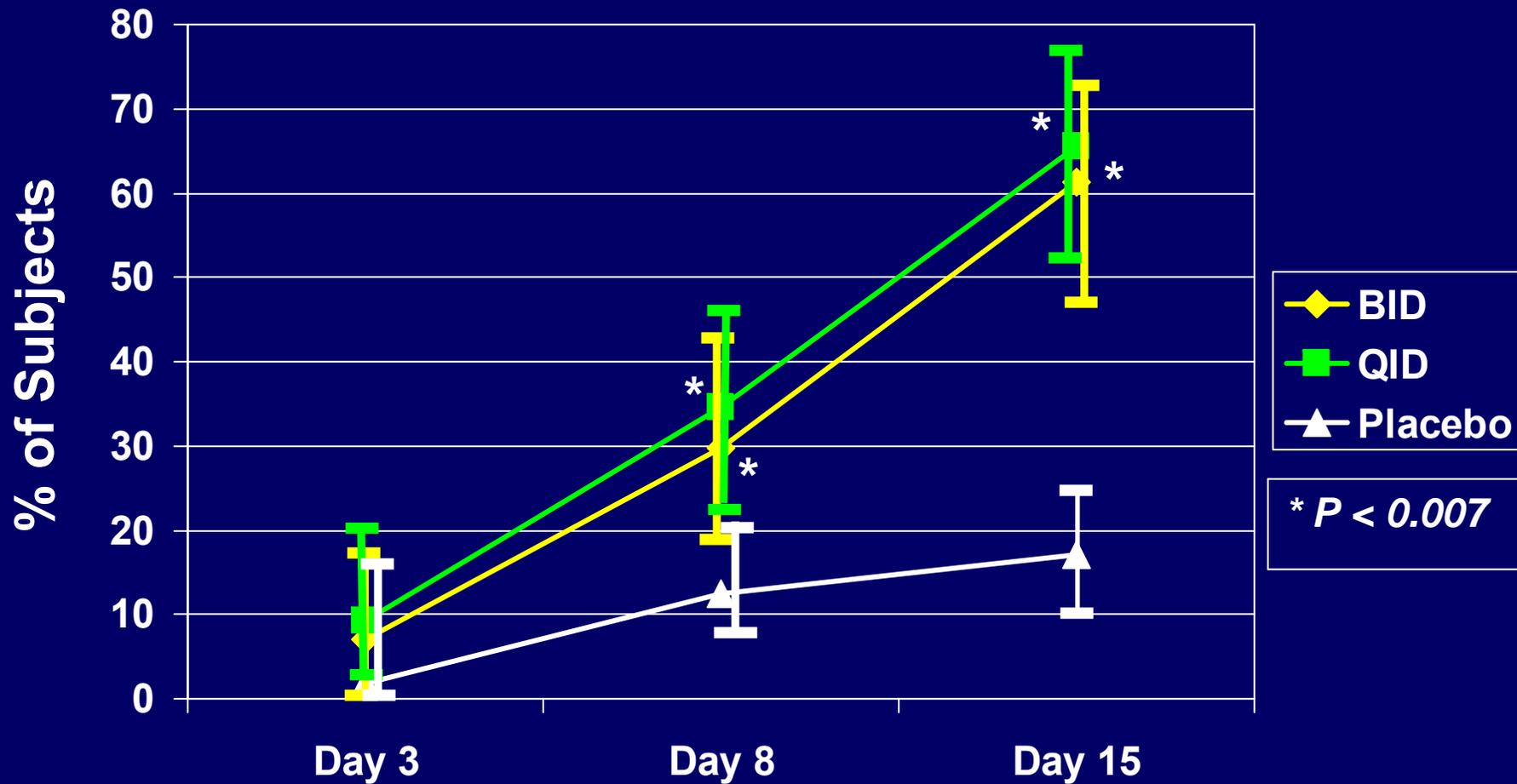
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Sirion Phase 3: AC Cell Grade = “0” BID vs Placebo

	BID	Placebo	P value
Study 1	N=57	N=105	
Day 3	7.0%	1.9%	<i>P</i> = 0.1126
Day 8	29.8%	12.4%	<i>P</i> = 0.0066
Day 15	61.4%	17.1%	<i>P</i> < 0.0001
Study 2	N=53	N=113	
Day 3	1.9%	1.8%	<i>P</i> = 0.8706
Day 8	30.2%	6.2%	<i>P</i> < 0.0001
Day 15	49.1%	15.0%	<i>P</i> < 0.0001

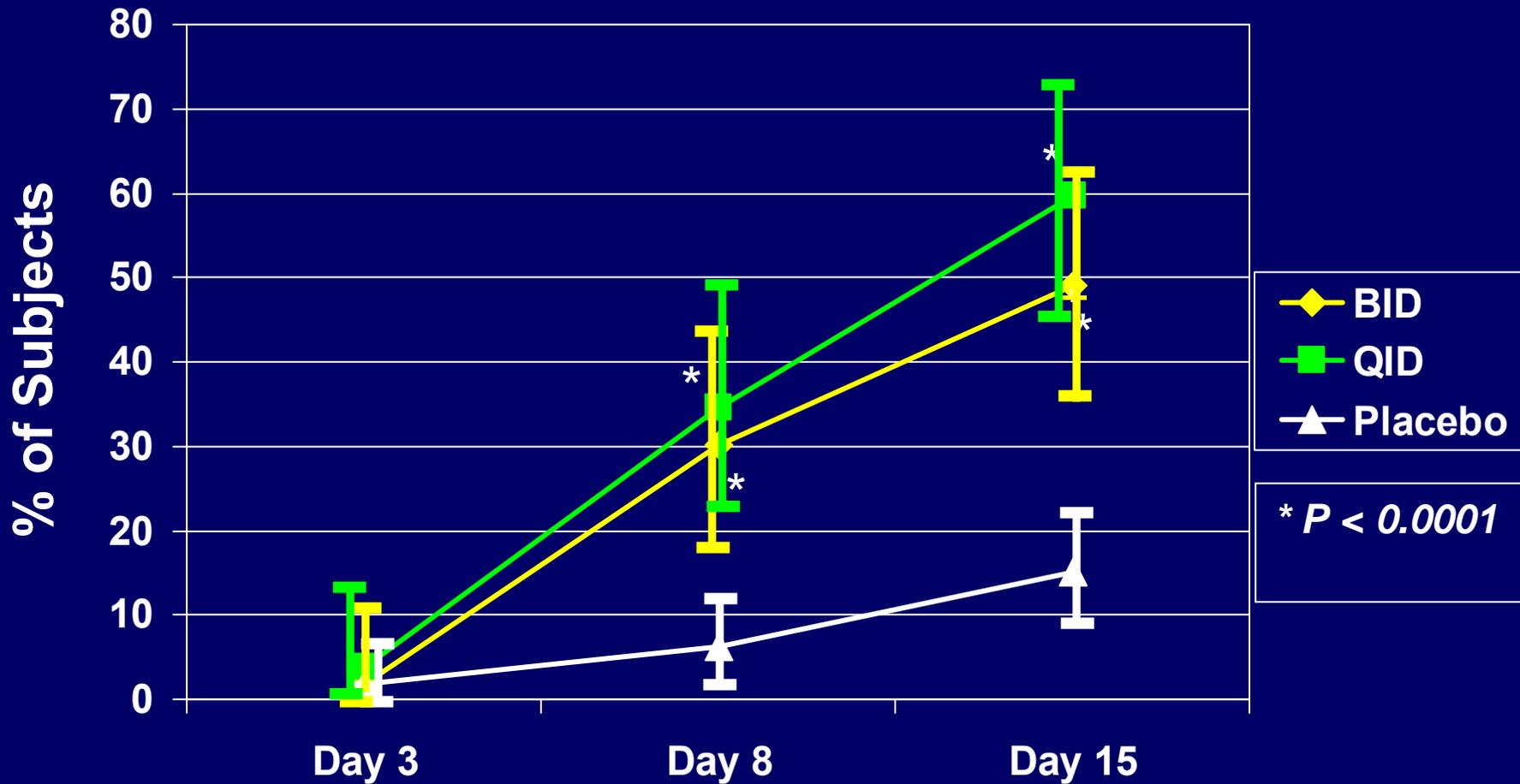
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Study 1: Percent of Subjects with AC Cell Grade = "0"



Upper and Lower 95% Confidence Limits

Study 2: Percent of Subjects with AC Cell Grade = "0"



Upper and Lower 95% Confidence Limits

Sirion Phase 3: AC Cell Grade = "0" QID and BID on Day 8

	QID	BID	Placebo
Study 1	N=55	N=57	N=105
	34.5%	29.8%	12.4%
<i>P value</i>	<i>0.0014</i>	<i>0.0066</i>	
Study 2	N=52	N=53	N=113
	34.6%	30.2%	6.2%
<i>P value</i>	<i>< 0.0001</i>	<i>< 0.0001</i>	

Adjusted by site; ITT, LOCF

Sirion Phase 3: AC Cell Grade = "0" QID and BID on Day 15

	QID	BID	Placebo
Study 1	N=55	N=57	N=105
	65.5%	61.4%	17.1%
<i>P value</i>	<i>< 0.0001</i>	<i>< 0.0001</i>	
Study 2	N=52	N=53	N=113
	59.6%	49.1%	15.0%
<i>P value</i>	<i>< 0.0001</i>	<i>< 0.0001</i>	

Adjusted by site; ITT, LOCF

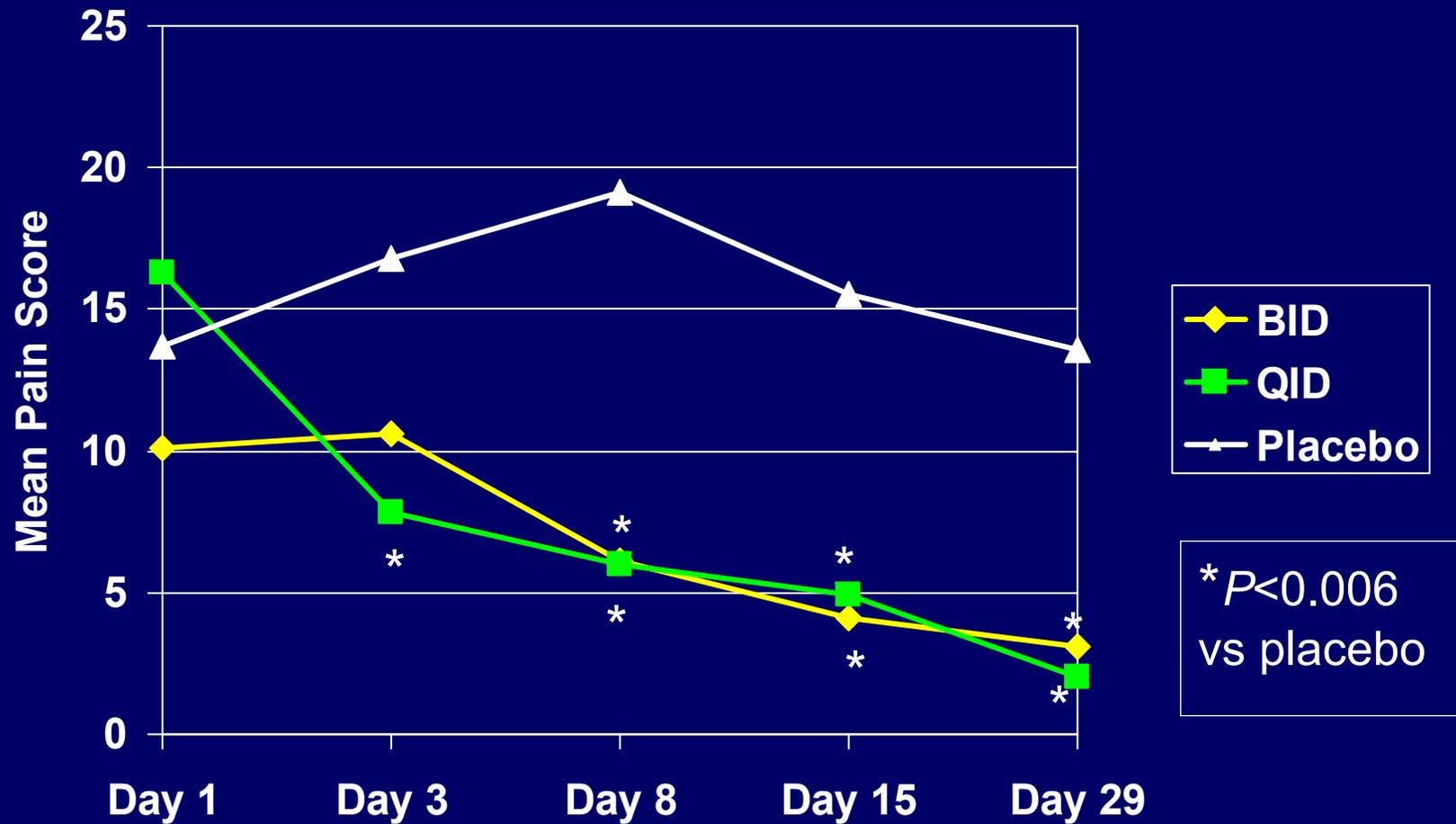
Sirion Phase 3: Pain Score = “0” (VAS) QID vs Placebo

	QID	Placebo	<i>P</i> value
Study 1	N=55	N=105	
Day 3	50.0%	27.6%	<i>P</i> = 0.0026
Day 8	69.1%	30.5%	<i>P</i> < 0.0001
Day 15	76.4%	44.8%	<i>P</i> = 0.0001
Study 2	N=52	N=113	
Day 3	40.4%	22.1%	<i>P</i> = 0.0116
Day 8	46.2%	23.9%	<i>P</i> = 0.0027
Day 15	48.1%	25.7%	<i>P</i> = 0.0021

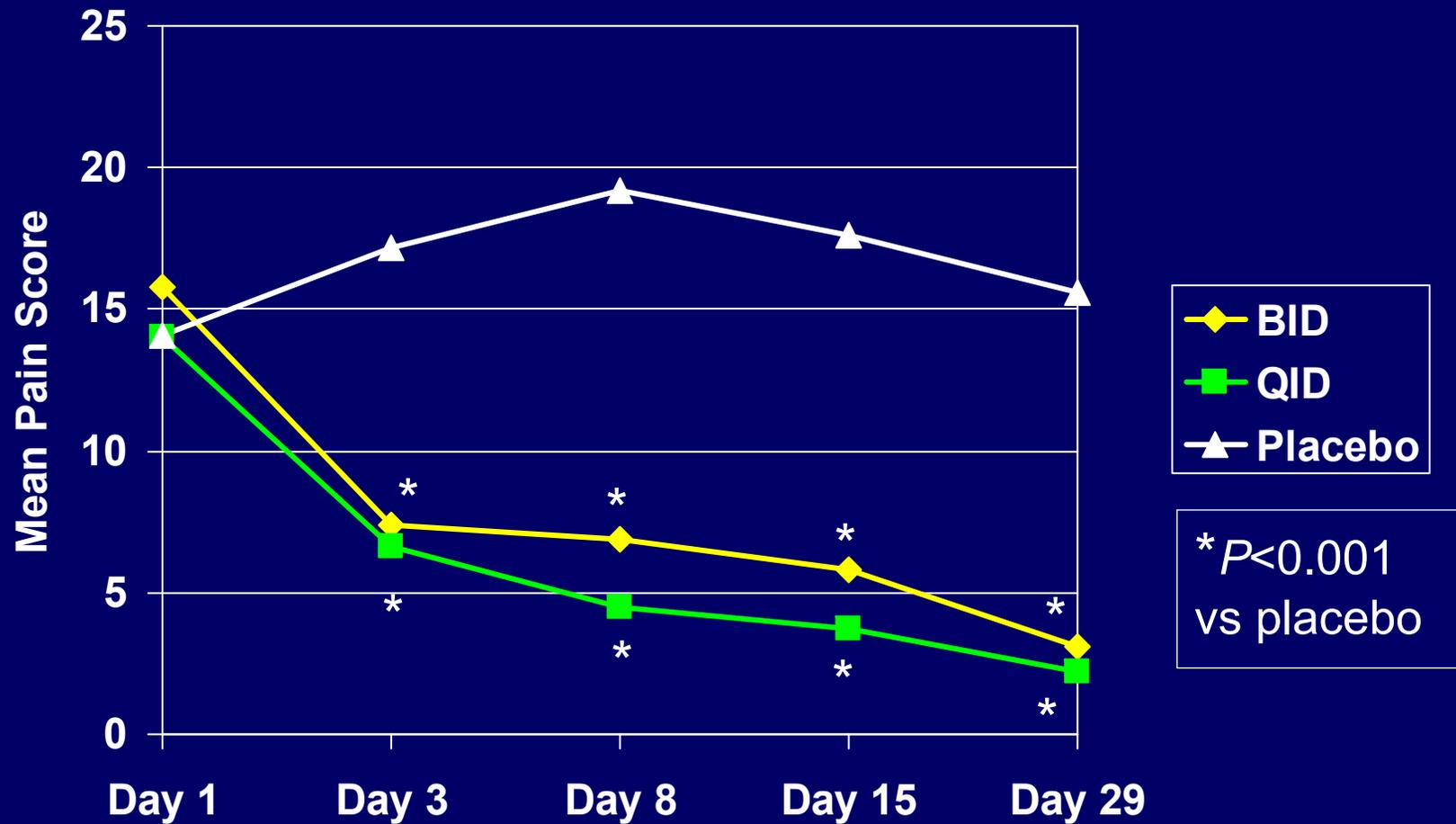
Sirion Phase 3: Pain Score = “0” (VAS) BID vs Placebo

	BID	Placebo	<i>P</i> value
Study 1	N=57	N=107	
Day 3	40.4%	27.6%	<i>P</i> = 0.0772
Day 8	40.4%	30.5%	<i>P</i> = 0.2250
Day 15	63.2%	44.8%	<i>P</i> = 0.0209
Study 2	N=54	N=113	
Day 3	35.8%	22.1%	<i>P</i> = 0.0800
Day 8	43.4%	23.9%	<i>P</i> = 0.0121
Day 15	43.4%	25.7%	<i>P</i> = 0.0150

Sirion Study 1: Mean Pain Score (VAS)



Sirion Study 2: Mean Pain Score (VAS)



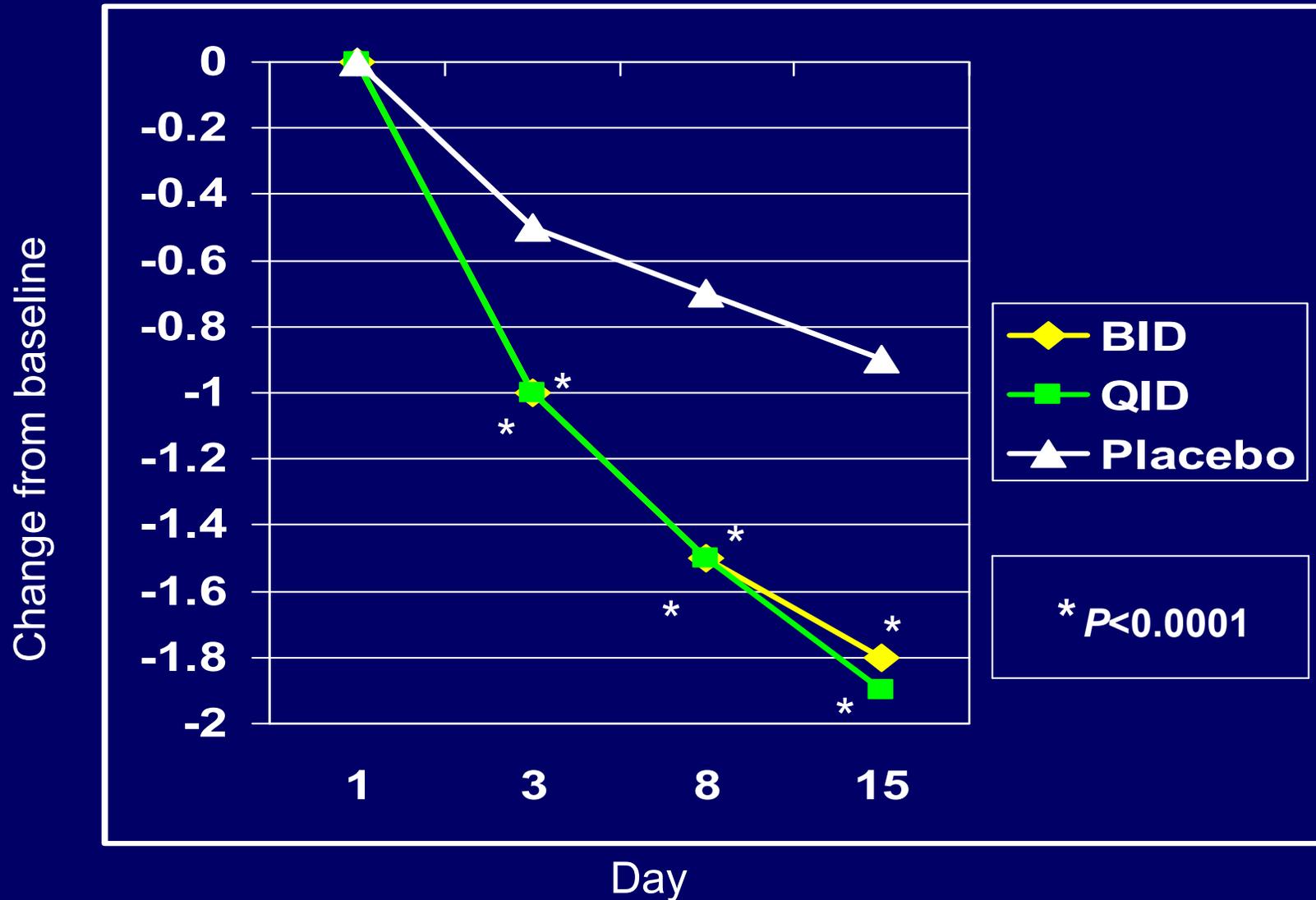
Sirion Phase 3: Additional efficacy analyses for clinical perspective

- Change from baseline in mean AC cell grade
- Clearing of inflammation (cell count ≤ 5 and flare grade = 0)
- Proportion of subjects withdrawn due to lack of efficacy

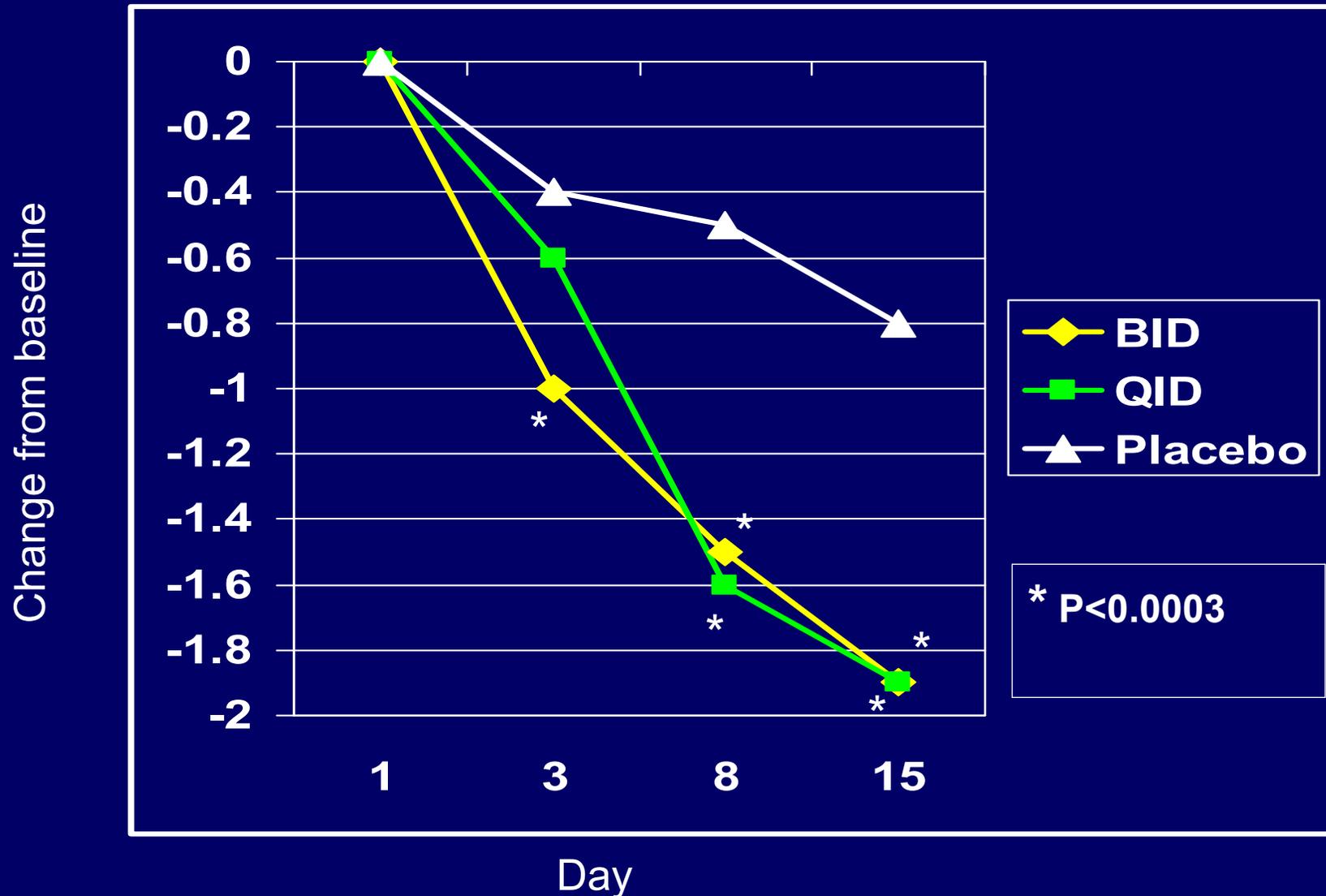
Sirion Phase 3: Change From Baseline in Mean AC Cell Grade

	BID	QID	Placebo	P Value BID Regimen	P value QID Regimen
Study 1	N=57	N=55	N=105		
Day 3	-1.0	-1.0	-0.5	< 0.0001	< 0.0001
Day 8	-1.5	-1.5	-0.7	< 0.0001	< 0.0001
Day 15	-1.8	-1.9	-0.9	< 0.0001	< 0.0001
Study 2	N=53	N=52	N=113		
Day 3	-1.0	-0.6	-0.4	0.0002	0.1360
Day 8	-1.5	-1.6	-0.5	< 0.0001	< 0.0001
Day 15	-1.9	-1.9	-0.8	< 0.0001	< 0.0001

Study 1: Mean Change From Baseline in AC Cell Grade



Study 2: Mean Change From Baseline in AC Cell Grade



Sirion Phase 3: Proportion of Subjects - Clearing of Inflammation (Cells ≤ 5 and Flare Grade = 0)

	BID	QID	Placebo	P Value BID Regimen	P value QID Regimen
Study 1	N=57	N=55	N=105		
Day 8	49.1%	50.9%	21.0%	< 0.0001	< 0.0001
Day 15	73.7%	70.9%	31.4%	< 0.0001	< 0.0001
Study 2	N=53	N=52	N=112		
Day 8	43.4%	32.7%	17.0%	0.0001	0.0118
Day 15	71.7%	71.2%	23.0%	< 0.0001	< 0.0001

Sirion Phase 3: Proportion of Subjects Withdrawn Due to Lack of Efficacy

	QID	BID	Placebo
Study 1	N=55	N=57	N=107
n (%)	1 (1.8%)	4 (7.0%)	33 (30.8%)
<i>P value</i>	<i>< 0.0001</i>	<i>0.0001</i>	

	QID	BID	Placebo
Study 2	N=52	N=54	N=113
n (%)	2 (3.8%)	5 (9.3%)	54 (47.8%)
<i>P value</i>	<i>< 0.0001</i>	<i>< 0.0001</i>	

Sirion Phase 3: Proportion of Subjects Successfully Completing Treatment

	QID	BID	Placebo
Study 1	N=55	N=57	N=107
	92.7%	91.2%	63.6%

	QID	BID	Placebo
Study 2	N=52	N=54	N=113
	92.3%	88.9%	49.6%

Sirion Phase 3: Overview of Efficacy

Difluprednate is effective for the treatment of inflammation and pain associated with ocular surgery

- ✓ Two Phase 3 placebo-controlled studies
- ✓ Statistically significant improvement in pain and inflammation as well as other endpoints
- ✓ On BID or QID subjects achieved cleared anterior chamber inflammation at Day 8 and Day 15
- ✓ Subjects who received placebo were more likely to withdraw from the study due to a lack of treatment effect
- ✓ BID dosing provides the lowest effective dose regimen
- ✓ Clinical evidence supports both BID and QID dosing

Overview of Safety

- Sirion Phase 3 AEs
- Ocular AEs $\geq 2\%$
- Mean IOP
- Clinically significant IOP increase
- Summary of safety

Sirion Phase 3: Safety Overview

	BID N=111 n (%)	QID N=107 n (%)	Placebo N=220 n (%)
Event Category			
SAEs	1 (0.9)	4 (3.7)	2 (0.9)
AEs Leading to Discontinuation	9 (8.1)	4 (3.7)	58 (26.4)
Deaths	0 (0.0)	0 (0.0)	1 (0.5)

Sirion Phase 3 SAEs

Note: No ocular SAEs reported in Sirion's Phase 3 studies

SAE	Treatment	Severity of Event	Relationship to Treatment
Atrial fibrillation	Difluprednate BID	Moderate	Not related
Dehydration	Difluprednate QID	Moderate	Not related
Pneumonia	Difluprednate QID	Moderate	Not related
Headache	Difluprednate QID	Severe	Not related
Urinary tract infection	Difluprednate QID	Severe	Not related
Stroke	Placebo	Severe	Not related
Respiratory distress	Placebo	Severe	Not related

Ocular SAEs Reported in Senju's Uveitis and Postsurgical Inflammation Studies (N = 207)

SAE/Onset	Treatment	Relationship to Study Drug
Maculopathy / Day 3	Study drug continued through Day 14. 90 days post last dose-vitreous displacement	Unrelated
Retinal Detachment / Day 13	Study drug continued through Day 15. Retinopexy at Day 19	Unrelated Result of vitreous surgery Resolved by Day 38
Iris Adhesions / Day 2	Study drug continued through Day 12. Posterior synechiotomy 5 days post last dose	Possibly related Resolved
Corneal Perforation / Day 6	Contralateral eye. Treatment of study eye continued for 14 days.	Unrelated Corneal herpes in the contralateral eye. Resolved
Necrotizing Retinitis / Day 13	Last dose – Day 13; Hospitalized on Day 13 (final day on study drug). Treatment with meds for 13 days.	Unrelated Underlying viral acute retinal necrosis Resolved

Sirion Phase 3: Ocular AEs \geq 2% Difluprednate > Placebo

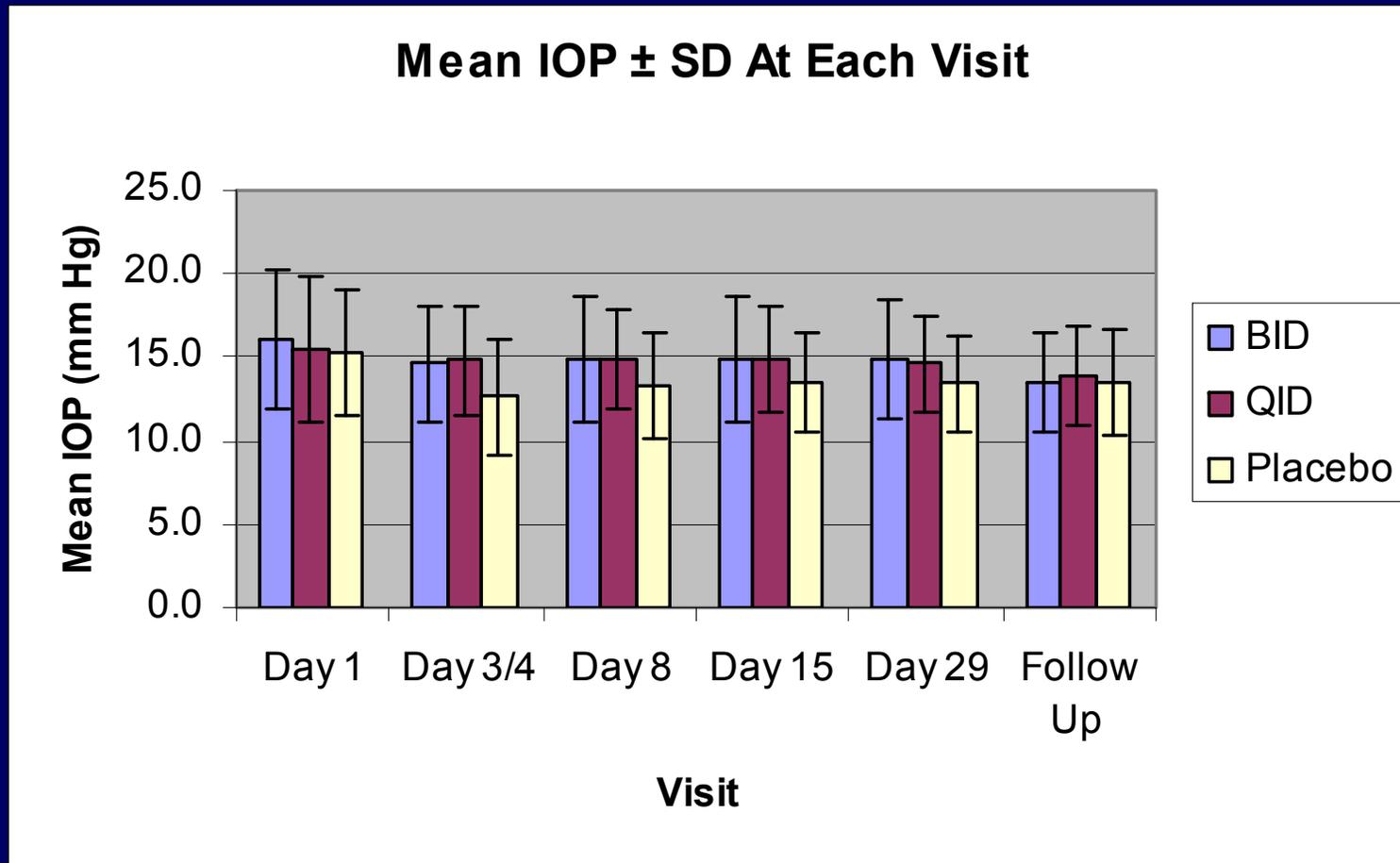
	BID (N=111)	QID (N=107)	Placebo (N=220)
Posterior capsule opacification	15.3	11.2	14.5
Punctate keratitis	7.2	5.6	3.6
IOP increase	2.7	1.9	0.9
Iritis	4.5	1.9	1.4
Vitreous detachment	2.7	1.9	1.8
Conjunctival hemorrhage	2.7	0.9	0.5

Sirion Phase 3: Ocular AEs \geq 2%

Placebo > Difluprednate

	BID (N=111)	QID (N=107)	Placebo (N=220)
Conjunctival hyperemia	9.9	15.0	34.5
Eye pain	10.8	4.7	20.0
Photophobia	9.9	9.3	20.5
Corneal edema	10.8	4.7	25.5
Ciliary hyperemia	5.4	9.4	28.2
Conjunctival edema	6.3	4.7	12.3
Reduced visual acuity	5.4	1.9	16.8
Eye inflammation	2.7	4.7	7.7
Foreign body sensation	2.7	1.9	7.3
Anterior chamber cell	4.5	3.7	18.2
Anterior chamber flare	2.7	0.9	14.1

Sirion Phase 3: Mean Intraocular Pressure



Summary of Clinically Significant IOP Increase

	Sirion Postsurgical Studies			Senju Postsurgical Studies	Senju Uveitis Studies	Total Studies
	Difluprednate BID N=111	Difluprednate QID N=107	Placebo BID+QID N=220	Difluprednate QID N=111	Difluprednate QID N=96	Difluprednate N=425
Clinically Significant IOP Increase	3 (2.7%)	3 (2.8%)	2 (0.9%)	6 (5.4%)	5 (5.2%)	17 (4.0%)

Subjects with an IOP increase ≥ 10 mm Hg from baseline and ≥ 21 mm Hg

Sirion Phase 3: Summary of Safety

Difluprednate has an acceptable safety profile for the treatment of inflammation and pain associated with ocular surgery

- ✓ No ocular SAEs
- ✓ Fewer ocular AEs reported for subjects in BID and QID groups compared with placebo
- ✓ Vast majority of AEs were related to the outcome of surgery
- ✓ A higher proportion of subjects in the placebo group withdrew from study due to an AE
- ✓ < 3% of subjects had a clinically significant IOP increase

Conclusions

Difluprednate ophthalmic emulsion, 0.05% is well tolerated and efficacious for the treatment of inflammation and pain associated with ocular surgery in both BID and QID dosage regimens

Supportive Slides

Sirion Phase 3: AC Cell Grade = “0” Plus Pain = 0 on Day 8

	QID	BID	Placebo
Study 1	N=55	N=57	N=104
	25.5 %	14.0%	8.7%
<i>P value</i>	0.0054	0.3345	

	QID	BID	Placebo
Study 2	N=52	N=53	N=113
	17.3%	18.9%	3.5%
<i>P value</i>	0.0011	0.0013	

Adjusted by site; ITT, LOCF

Sirion Phase 3: AC Cell Grade = "0" Plus Pain = 0 on Day 15

	QID	BID	Placebo
Study 1	N=55	N=57	N=104
	54.5%	42.1%	10.6%
<i>P value</i>	<i><0.0001</i>	<i><0.0001</i>	
Study 2	N=52	N=53	N=113
	36.5%	28.3%	7.1%
<i>P value</i>	<i><0.0001</i>	<i>0.0002</i>	

Adjusted by site; ITT, LOCF

Senju Phase 3 Postsurgical Inflammation: Mean IOP

Study Day	Difluprednate	Betamethasone
	QID N=98	QID N=98
	Mean \pm SD (mm Hg)	Mean \pm SD (mm Hg)
Day -1 (day before surgery)	13.3 \pm 3.1	13.0 \pm 2.8
Day 1 (day after surgery)	14.5 \pm 5.0	14.3 \pm 4.7
Day 3	12.8 \pm 4.4	11.4 \pm 3.9
Day 7	13.2 \pm 5.0	12.0 \pm 4.0
Day 14	14.2 \pm 4.8	12.6 \pm 3.7
