

Efficacy and safety of different doses of a slow release corticosteroid implant for macular edema

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Dear editor

I read “Efficacy and safety of different doses of a slow release corticosteroid implant for macular edema: meta-analysis of randomized controlled trials” published in May 2015 by Liu et al.¹ The purpose of this article was to report the meta-analysis for the efficacy and safety of intravitreal corticosteroid implants for macular edema. However, there are some factual errors which mean the current article is misleading and these errors need to be pointed out to the readers of *Drug Design, Development and Therapy*.

First point – from the title of the article, the reader is expecting to read about corticosteroids that are licensed for use for macular edema. At this point the author should have specified that the therapy area being reviewed is diabetic macular edema (DME) and that Retisert (fluocinolone acetonide) is not licensed for this indication.² ILUVIEN® (190 micrograms fluocinolone acetonide intravitreal implant in applicator) and Ozurdex (dexamethasone),³ however, are indicated for the treatment of DME.

Second point – ILUVIEN now has marketing authorizations in Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, and the United Kingdom for the treatment of vision impairment associated with chronic DME, considered insufficiently responsive to available therapies.⁴ Contrary to the statement in the “Discussion”, in November 2014 ILUVIEN was approved by the US Food and Drug Administration for the treatment of DME in patients who have previously been treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.⁵ Hence there are slight differences between the European and USA licenses (these are summarized in Table 1).

Third point – in Europe the license for ILUVIEN is based on efficacy data reported at 36 months in the FAME trials.⁶ In Table 1 the authors cite Retisert, which is not the name of the licensed medicine, and support this with data from Campochiaro et al published in 2011. However, this is misleading as the study cited was performed with ILUVIEN and has now been superseded by Campochiaro et al in 2012 which reports the 3-year results.⁶

Fourth point – the authors refer to the efficacy and safety data for ILUVIEN and Ozurdex but have not accurately presented the current data and corrected the data to reflect USA and European licensed data. Table 1 has been generated to help the reader understand the differences between pivotal trial data for ILUVIEN and Ozurdex^{6,7} and the licensed indications for ILUVIEN in the USA and Europe.^{6,7}

In conclusion, it is hoped that the inaccuracies that have been identified will help clarify that ILUVIEN® is an approved therapy for the treatment of DME and available

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Table 1 Summary of the pivotal trial data for ILUVIEN and Ozurdex

Heading		Ozurdex		ILUVIEN	
Disease area		DME		Chronic DME (European license)	DME (US FDA label)
Active		Dexamethasone (DEX)		Fluocinolone acetonide (FAC)	
Formulation		Biodegradable		Non-bioerodible (polyimide tube)	
Dose		700 µg		190 µg	
Release rate		6 µg DEX per day		0.2 µg FAC per day	
Phase III clinical trial in DME		206207-010 and 011		FAME trials (FAME A and B)	
a. Description of studies.		a. Two identically designed Phase III trials (206207-010 and 011) that were randomized, masked and sham-controlled.		a. The FAME trials were performed under a single protocol as randomized, double-masked, sham injection-controlled, parallel-group, multicenter studies conducted over a 36-month period and included a pre-planned subgroup analysis to assess efficacy in chronic DME patients.	
b. The primary endpoint.		b. The primary endpoint for these studies at the end of 36 months was the average change in BCVA from baseline with one of the trials failing to reach its primary endpoint.		b. The primary endpoint in the FAME trials was 24 months. The secondary endpoint was at 36 months (and the basis for the license and indication approved in Europe). Both FAME trials independently met their primary efficacy endpoints of ≥ 15 letter improvement in BCVA over baseline.	
c. The number of patients studied in the studies.		c. A total of 1,048 subjects were randomized.		c. A total of 956 subjects were randomized.	
Efficacy					
Percentage of patients gaining ≥ 15 letters at 24 and 36 months		36 months: 22.2% vs 12.0% (6 µg DEX vs sham control) [difference vs sham control =10.2%]		24 months: 34.4% vs 13.4% (0.2 µg FAC vs sham control) [difference vs sham control =21.0%] 36 months: 34.0% vs 13.4% (0.2 µg FAC vs sham control) [difference vs sham control =20.6%]	24 months: 28.7% vs 16.2% (0.2 µg FAC vs sham control) [difference vs sham control =12.5%] 36 months: 28.7% vs 18.9% (0.2 µg FAC vs sham control) [difference vs sham control =9.8%]
Mean BCVA		*36 months: 3.5 vs 2.0 letters (6 µg DEX vs sham control) [difference vs sham control =1.5 letters]		24 months: +6.0 vs 2.2 letters (0.2 µg FAC vs sham control) [difference vs sham control =3.8 letters] 36 months: +7.6 vs 1.8 letters (0.2 µg FAC vs sham control) [difference vs sham control =5.8 letters]	24 months: +4.4 vs 1.7 letters (0.2 µg FAC vs sham control) [difference vs sham control =2.7 letters] 36 months: +5.3 vs 2.0 letters (0.2 µg FAC vs sham control) [difference vs sham control =2.3 letters]
Duration of action of one injection		Up to 6 months		Up to 36 months	
Safety					
a. Cataract-related adverse events		67.9% vs 20.4% (6 µg DEX vs sham control) [difference vs sham control =47.5%]		86.0% vs 51.5% (0.2 µg FAC vs sham control) where cataract was considered an adverse event [difference vs sham control =34.5%]	81.7% vs 50.4% (0.2 µg FAC vs sham control) where cataract was considered an adverse event [difference vs sham control =31.3%]
b. Cataract-related extraction		59.2% vs 7.2% (6 µg DEX vs sham control) [difference vs sham control =52.0%]		85.1% vs 36.4% (0.2 µg FAC vs sham control) where cataract was considered an adverse event [difference vs sham control =48.7%]	80.0% vs 27.3% (0.2 µg FAC vs sham control) where cataract was considered an adverse event [difference vs sham control =52.7%]

c. Elevated IOP	41.5% vs 9.1% (6 µg DEX vs sham control) required IOP-lowering drops [difference vs sham control =36.0%]	35.9% vs 15.2% (0.2 µg FAc vs sham control) required IOP-lowering drops [difference vs sham control =20.7%]	38.4% vs 14.1% (0.2 µg FAc vs sham control) required IOP-lowering drops [difference vs sham control =24.3%]
d. Underwent IOP-lowering surgery	0.6% vs 0.0% (6 µg DEX vs sham control) [difference vs sham control =0.6%]	*5.3% vs 0.0% (0.2 µg FAc vs sham control) underwent IOP-lowering surgery [difference vs sham control =5.3%]	*4.8% vs 0.5% (0.2 µg FAc vs sham control) underwent IOP-lowering surgery [difference vs sham control =4.3%]

Notes: #Average change from baseline and calculated using area under curve approach. *In patients previously treated with an ocular steroid injection, none underwent IOP-lowering surgery and all IOP-lowering surgeries in subjects treated with ILUVIEN[®] occurred in patients having no history of ocular steroid injection.^{6,7}

Abbreviations: BCVA, best-corrected visual acuity; IOP, intraocular pressure; DME, diabetic macular edema; US FDA, US Food and Drug Administration.

in 17 European countries and also the USA. Moreover, there are differences between the use of ILUVIEN in Europe and the USA as well as between ILUVIEN and Ozurdex, both corticosteroids licensed for DME, and these differences are detailed in Table 1 to help avoid any unnecessary confusion.

Disclosure

The author is a consultant in medical affairs to Alimera Sciences in Europe.

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Authors' reply

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Dear editor

Thank you for your letter. We really appreciate your rigor and conscientiousness. We will give a response one by one.

First point – in our selection criteria, we list the criteria, “inclusion of a comparison of different doses of any intravitreal corticosteroid implant for the treatment of any type of ME [macular edema]”. In Campochiaro et al's research, the fluocinolone acetonide vitreous inserts were used for diabetic macular edema.¹

Second point – Dr Hall states that ILUVIEN® was approved by the US Food and Drug Administration in November 2014, which was contrary to our “Discussion”. However, in our literature search, we mentioned that, “A systematic English language search was conducted from inception to November 2014”.² “ILUVIEN® is approved for use in several European countries (Austria, France, Germany, Portugal, and Spain and is pending approval in Italy) for the treatment of impairment of vision associated with chronic diabetic macular edema that is insufficiently responsive to available therapies. It has yet to receive approval by the FDA for use in the United States”.³

Third point – we have mistaken the fluocinolone acetonide (FA) intravitreal inserts for Retisert, both of which were loaded with FA. We regret that and we will submit a

corrigendum. We thank Dr Hall for pointing that out. Both of the studies by the FAME Study Group were included in our first 14 reports. The identifiers of the two researches registered at www.clinicaltrials.gov are the same: NCT 0034968, which means most of these data and patients were the same. To avoid bias and repeat of data analysis, we chose the report published in 2011,¹ which had the lower percentage of patients who failed to remain in the study at the endpoint and a larger sample.

Fourth point – the purpose of our meta-analysis was to assess the efficacy and safety of intravitreal corticosteroid implants for macular edema. Data were extracted from each included report published before November 2014. Different study groups conducting these included randomized controlled trials in dozens of countries. We analyzed these data synthetically instead of subdividing by different area. We really appreciate Dr Hall's carefulness. The table is perspicuous, clarifying the indication and management of these sustained-release corticosteroid options.

Disclosure

The authors have no conflict of interest in this communication.

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