ALLERGAN

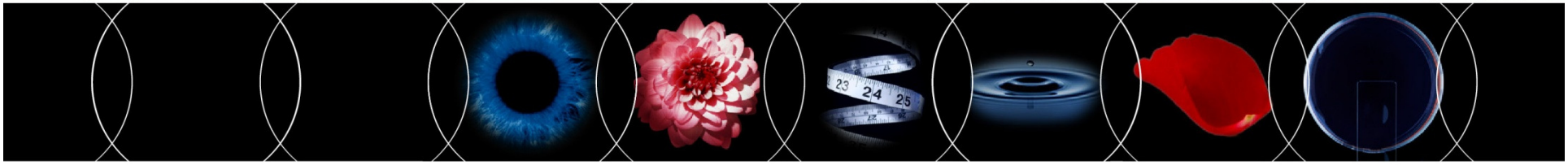
Our pursuit. Life's potential.™

EU Regulatory workshop – Ophthalmology – clinical development and scientific advice. Industry view on DME and macular edema secondary to RVO

Yehia Hashad, M.D.

Vice President and Global Therapeutic Area Head

Retina



Introduction to diabetic macular edema

- Diabetic macular edema (DME), is a multi-factorial disease secondary to persistent hyperglycemia, leads to up regulation of growth factors which if untreated results in retinal fibrosis and severe vision loss.
- DME is the leading cause of blindness in the working population over 50 years. *(Diabetes Care 2003; 26: 99-102; Nature 2001; 414:782–787, Br J Ophthalmol 2001; 85: 354-356)*
- Until recently the standard of care (SoC) was laser photocoagulation which slows progression of vision loss; however, with this treatment vision improvement is an uncommon event even after 3 years of treatment.
- Ranibizumab (Lucentis), recently approved by EMA to treat patients with vision impairment secondary to DME, has been shown to improve vision. *Assessment Report For Lucentis, EMEA/H/C/000715/II/0020, 21st October 2010 (Approved 6th January 2011)*
- Data from phase III studies for fluocinolone acetonide vitreous inserts and phase II study for VEGF trap eye have been published. *(Ophthalmology 2011;118:626-635 and Ophthalmology 2011;118:1819-1826)*

Introduction to retinal vein occlusion

- RVO (Retinal Vein Occlusion) is second only to diabetic retinopathy as a cause of visual loss due to retinal vascular disease. There are two forms of retinal vein occlusion:
  - *Branch Retinal Vein Occlusion* (BRVO) – blockage of the blood flow through the branches of the central retinal vein, typically secondary to hardened overlying retinal artery. Laser treatment is used for BRVO.
  - *Central Retinal Vein Occlusion (CRVO)* - blockage of the blood flow through central retinal vein; resulting in marked decrease in vision , which may improve over many months without treatment. There are two forms; Ischemic (30%) & non-ischemic (70%) *(Current eye research, 33:111-131, 2008)*
- Until recently the SoC was observation in CRVO and selected cases of BRVO and focal laser photocoagulation in other BRVO.
- Ozurdex and Lucentis have been approved (EMA) for the treatment of macular edema secondary to BRVO and CRVO *Assessment Report For Lucentis, EMA/392690/2011, 17th March 2011 (Approved 27th May 2011)*

Discussion Topics

- Target population
- Endpoints
- Comparator
- Duration of clinical trials
- Combination therapies
- Overall development strategies

Published pivotal studies used in this presentation

- **RESOLVE study:** a 12 month, randomized, controlled, double masked, multicentre phase II study of Ranibizumab in DME *(Diabetes care, 33:2399-2405, 2010)*
- **THE RESTORE study:** a 12 month, randomized, double masked multicentre, phase III study of Ranibizumab monotherapy or combined with laser versus Laser monotherapy for DME *(Ophthalmology 2011;118:615-625)*
- **FAME studies:** two parallel, randomized, sham injection-controlled, double masked multicentre phase III studies of sustained-delivery Fluocinolone Acetonide vitreous inserts for DME *(Ophthalmology 2011;118,626-635)*
- **THE DA VINCI study:** a randomized, double-masked, multicentre phase 2 trial of VEGF Trap-eye for DME*(Ophthalmology 2011;118:1819-1826)*
- **BRAVO study:** a 6 month, randomized, double-masked, multicentre, sham-controlled, phase III study of Ranibizumab for macular edema secondary to BRVO *(Ophthalmology 2010;117:1102-1112)*
- **CRUISE study:** a 6 month, randomized, double-masked, multicentre, sham-controlled, phase III study of Ranibizumab for macular edema secondary to CRVO *(Ophthalmology 2010;117:1124-1133)*
- **GENEVA studies:** two parallel, 6 month, randomized, double-masked, multicentre, sham-controlled, phase III studies of Dexamethasone intravitreal implant for macular edema secondary to RVO *(Ophthalmology 2010;117:1134-1146)*

Target population in DME studies

	Ranibizumab (RESOLVE study)	Ranibizumab (RESTORE study)	Fluocinolone Acetonide Insert (FAME studies)	VEGF trap eye (DA VINCI study)
BCVA	73-39 letters (20/40 to 20/160)	78-39 letters (20/32 and 20/160)	69-19 (20/50 - 20/400)	73-24 (20/40 – 20/320)
OCT	Central macular thickness ≥300 µm	Any edema in the center subfield that is causing decrease in VA	Central macular thickness $\geq$ 250 despite prior focal/grid macular laser	Central retinal thickness ≥250 µm
HbA1C	≤12 %	≤10 %	-	Patients with uncontrolled diabetes were excluded
Prior treatments (Laser / pharmacologic treatments)	Conditionally allowed	Conditionally allowed	-	Conditionally allowed
Type of DME	Focal & diffuse	Focal & diffuse	Focal & diffuse	Focal & diffuse

Target population in RVO studies

	Ranibizumab (BRAVO study)	Ranibizumab (CRUISE study)	DEX implant (GENEVA studies)
BCVA	73 - 24 letters (Snellen equivalent s 20/40 – 20/320)	73 - 24 letters (Snellen equivalent s 20/40 – 20/320)	68-34 letters (Snellen equivalent 20/50 - 20/200)
OCT	Mean central subfield thickness ≥ 250 µm	Mean central subfield thickness ≥ 250 µm	Mean central subfield thickness ≥ 300 µm
Duration of macular edema	Centre involved macular edema diagnosed within 12 months of study initiation	Centre involved macular edema diagnosed within 12 months of study initiation	Centre involved macular edema diagnosed between 6 wks and 9 months of CRVO and between 6 wks and 12 months of BRVO diagnosis
Prior treatments (Laser / pharmacologic treatments)	Conditionally allowed	Conditionally allowed	Conditionally allowed

Target population for DME & RVO studies

- There are no issues related to the target population. There is a need for flexibility in the design of the clinical studies specially to accommodate for the advances in technology and facilitate recruitment.
- However, a key message here that results from one study should not be compared to the other for the following reasons:
  - BCVA limits are different across studies which may impact study results
  - OCT instrumentation types are different and consequently measurements of thickness will vary.
  - Duration of macular edema prior to enrollment could affect the study results.
  - Using different definitions in certain sub-populations (e.g. focal vs. diffuse edema or definition of ischemic Vs. non ischemic cases) could lead to different results.
  - Proportion of patients with prior laser treatment varies from one study to the other.

Endpoints of published pivotal studies

ALLERGAN

Pivotal DME studies

	Ranibizumab (RESOLVE study)	Ranibizumab (RESTORE study)	Fluocinolone Acetonide Insert (FAME studies)	VEGF trap eye (DA VINCI study)
Primary Endpoint	Mean average change in BCVA from baseline to month 1 through 12 (AUC approach)	Mean average change in BCVA from baseline to month 1 through 12 (AUC approach)	Percentage of patients with ≥15 letters improvement in BCVA at month 24 (responder analysis)	Mean change in BCVA from baseline to week 24

Pivotal RVO studies

	Ranibizumab (BRAVO study)	Ranibizumab (CRUISE study)	DEX PS DDS (GENEVA studies)
Primary Endpoint	Mean change in BCVA from baseline to Month 6	Mean change in BCVA from baseline to Month 6	Time to achieve a 15 letter improvement from baseline BCVA

Issues related to the primary endpoint of the study

The issue	Proposed solution	Pros	Cons
Some endpoints are evaluated at specific time points, others are mean change over time.	Assess the primary efficacy endpoint based on area under the curve approach (AUC)	Takes into consideration multiple treatments effect and long duration of treatment The approval of ranibizumab in DME with this endpoint establishes a precedent Mean change over time is a widely used and accepted endpoint in other therapeutic area.	There is no consensus on what would be a clinically meaningful value for this endpoint AUC may differ if measured over 1 year vs 2 years
Current therapies in DME & RVO impose a heavy treatment burden on patients and clinical centers. Could reduction of treatment burden become a valid endpoint for new therapies?	consider the reduction of treatment burden as evidence of product superiority if the effect of the test product on BCVA is non-inferior to SoC To provide guidance on what threshold can be used for reduction in treatment burden.	Having a standardized clear guidance on reduction of the treatment burden as an endpoint. Demonstrate additional benefit to the comparator (SoC) if non inferiority is met.	It does not reflect superiority in efficacy or safety
Definition of non-inferiority margin for non-inferiority studies.(NI)	NI margin should be determined based on the effect size of the drug vs. placebo as reported from previous studies. A common definition is 50% of the lower bound of CI from these previous studies	To introduce a standardized approach.	

Comparators of published pivotal studies

ALLERGAN

Pivotal DME studies

	Ranibizumab (RESOLVE study)	Ranibizumab (RESTORE study)	Fluocinolone Acetonide Insert (FAME studies)	VEGF trap eye (DA VINCI study)
Comparator	Sham	Laser	Sham	Laser

Pivotal RVO studies

	Ranibizumab (BRAVO study)	Ranibizumab (CRUISE study)	DEX PS DDS (GENEVA study)
Primary Endpoint	Sham, deferred laser	sham	sham

Issues related to the comparators

- There is a guideline from EMA *(CPMP/ICH/364/96)* which describes in details the choice of control group in clinical trials which considers many factors among which is the ethical and practical issues associated with the use of control arms

- Laser treatment
  - Laser has been the SoC for treatment of DME and ME secondary to BRVO and sham treatment (observation) for ME secondary to CRVO for many years; with the approval of pharmacologic treatments that can produce an immediate improvement of vision, is there a role for laser treatment or sham treatment as a monotherapy comparator in future pivotal clinical studies?

Duration of pivotal clinical studies in DME & RVO

ALLERGAN

Pivotal DME studies

	Ranibizumab (RESOLVE study)	Ranibizumab (RESTORE study)	Fluocinolone Acetonide Insert (FAME studies)	VEGF trap eye (DA VINCI study)
Study duration	12 months	12 months primary endpoint with additional 24 months safety extension	24 months primary endpoint with additional 12 month safety extension	This is a phase II study with 24 weeks primary endpoint and duration

Pivotal RVO studies

	Ranibizumab (BRAVO study)	Ranibizumab (CRUISE study)	DEX PS DDS (GENEVA study)
Study duration	6 months primary endpoint with additional 6 months extension	6 months primary endpoint with additional 6 months extension	6 months primary endpoint with additional 6 months extension

Issues related to duration of pivotal studies in DME and RVO

- For RVO there is a general consensus on the acceptability of a 6 month primary endpoint with additional 6 months for safety follow up .
- For DME, while the total duration of the registrational studies were nearly identical, there was considerable variation in the timing of the primary endpoint (12 months & 24 months)
- There is no clear guidance on the timing of the primary endpoint for the DME indication and whether this is due to:
  - Product is a NME or a known molecule?
  - The nature and therapeutic class of the product?
  - This is the first or a subsequent indication?
  - Other factors e.g. availability of SoC or test product provide unprecedented benefit ?
  - Frequency of treatment and number of injections during a certain period?
- Proposal : to have consensus on primary endpoint of 12 months with a 12 months safety extension in DME studies.
- Pros: there is precedent with the Lucentis approval

Use of combination therapy in DME and RVO pivotal studies

ALLERGAN

Pivotal DME studies

	Ranibizumab (RESOLVE study)	Ranibizumab (RESTORE study)	Fluocinolone Acetonide Insert (FAME studies)	VEGF trap eye (DA VINCI study)
Combination therapy	-	Combination of Lucentis and laser photocoagulation	-	-

Pivotal RVO studies

	Ranibizumab (BRAVO study)	Ranibizumab (CRUISE study)	DEX PS DDS (GENEVA studies)
Combination therapy	-	-	-

Issues related to combination therapy in DME and RVO studies

- Only one pivotal study tested combination of ranibizumab and laser photocoagulation in their clinical development. There was no additional benefit of the combination treatment when compared to the ranibizumab monotherapy arm over 12 months period.

- There is a guidance from EMA *(CHMP/EWP/240/95 rev.1 Feb.2009)* on the use of fixed and non-fixed pharmacologic dose combinations however what is not clear is:
  - Is there guidance from a regulatory perspective on:
    - Combination of 2 pharmacologic agents versus a combination of pharmacologic agent and a procedure (e.g. laser, PDT)?
    - Same day combinations versus add-on therapy i.e. the two treatments are separated by relatively long duration (1 month)
    - Duration of follow-up for combination studies?

- Proposal : to have more tailored guidance on the combinations for ophthalmic studies specially when there is a combination of a pharmacologic agent versus a non pharmacologic procedure.

Overall development strategies for approved or submitted products in DME and RVO

ALLERGAN

Pivotal DME studies

	Ranibizumab (RESOLVE study)	Ranibizumab (RESTORE study)	Fluocinolone Acetonide Insert (FAME studies)
Development strategy	A 12 month, phase II multicentre, sham controlled, double-masked study	A 12 month, phase III randomized, double-masked, multicentre, laser-controlled study	Two, phase III, parallel, prospective randomized, sham injection-controlled, double-masked, multicentre clinical trials

Pivotal RVO studies

	Ranibizumab (BRAVO study)	Ranibizumab (CRUISE study)	DEX PS DDS (GENEVA studies)
Development strategy	Prospective, Phase III, randomized, sham injection-controlled, double masked, multicentre clinical trial in patients with macular edema secondary to branch retinal vein occlusion	Prospective, phase III, randomized, sham injection-controlled, double masked, multicentre clinical trial in patients with macular edema secondary to central retinal vein occlusion	Two identical, multicentre, masked, randomized, 6-month, sham-controlled clinical trials (each include patients with BRVO and patients with CRVO)

Issues related to the overall development strategy for DME and RVO

- Different development strategies have been used to gain approval for different products in RVO
  - Lucentis was approved using one study for patients with branch retinal vein occlusion and another study for patients with central retinal vein occlusion.
  - Ozurdex was approved using two identical study each of which included patients with branch retinal vein occlusion and patients with central retinal vein occlusion.
- Are both development strategies acceptable in future clinical programs?

Conclusions

- Flexibility in inclusion and exclusion criteria should always be considered in designing clinical studies, however, caution should be practiced when extrapolating results of one study to the other.
- Consensus is needed for endpoints that take into consideration multiple treatment effects and long duration of studies. There is also a need for guidance on the use of reduction in treatment burden as an endpoint specially if comparative efficacy and safety of products are non-inferior.
- There are variations in the timing of the primary endpoint in the DME studies, our proposal is to have consensus on primary endpoint of 12 months with a 12 months safety extension in future DME studies.
- The role of laser or sham treatments as a monotherapy comparator should be re-evaluated in future studies.
- More ophthalmology tailored guidance on the combination of a pharmacologic agent with a non-pharmacologic procedure is required.
- Clarity from the regulatory perspective on the acceptance of having both CRVO and BRVO populations in same study versus two separate studies