Final study report

Intravitreal ranibizumab for the treatment of persistent diabetic vitreous hemorrhage: a randomized, double-masked, placebo-controlled feasibility study

Study acronym:	**PARADISE**
EudraCT:	2009-015559-25
REC number:	09/H0803/117
Co-Sponsors:	Kings College Hospital NHS Foundation Trust Kings College London
IMP:	Ranibizumab
Indication studied:	Persistent diabetic vitreous hemorrhage
Study design:	Randomized, double-masked, placebo-controlled feasibility study
Study initiation date:	28/09/2010
Date of early termination:	N/A
Chief Investigator:	Timothy L. Jackson PhD, FRCOphth School of Medicine King's College London Department of Ophthalmology King's College Hospital London SE5 9RS United Kingdom

Date of Report: 09/08/2017

The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including, but not limited to, the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments

SYNOPSIS

Study Title	Intravitreal ranibizumab for the treatment of persistent diabetic vitreous hemorrhage: a randomized, double-masked, placebo-controlled feasibility study
Study Centres	Kings College Hospital Guys and St Thomas' Hospitals
First patient's first visit	30/11/2010
Last patient's last visit	20/10/2015
Last dose of IMP taken by a subject	16/09/2014
Date of early termination	N/A
Design summary	The PARADISE study was an investigator-initiated, two-center, two-group, double-masked, placebo-controlled, randomized, feasibility study sponsored by a United Kingdom university hospital (ClinicalTrials.gov identifier: NCT01030770). Multicenter research ethics committee approval was obtained to cover both sites, all participants provided written informed consent and the study was conducted in accordance with the tenants of the Declaration of Helsinki.
Primary objective	To determine if preoperative intravitreal ranibizumab (Lucentis) can promote clearance of persistent diabetic heamorrhage and thereby avoid or delay therapeutic pars plana vitrectomy.
Secondary objectives	1. Number of patients requiring pars plana

	vitrectomy at study end 2. Mean duration from baseline to primary pars plana vitrectomy 3. Number of intraocular procedures required 4. Mean EDTRS visual acuity 5. Mean grade of vitreous haemorrhage (Grade 0-4) assessed using masked independent reading of fundus photographs, at 6 weeks after the Lucentis or placebo injection 6. Surgical complications 7. Grading of lens clarity using LOCS II (Lens Opacities Classification System version II)
Primary endpoint	The primary outcome measure was number of participants deemed to require vitrectomy at week 7, as assessed at the visit 6 weeks after ranibizumab/placebo.
Secondary endpoints	Secondary outcome measures were the number of participants requiring vitrectomy at the study end; mean duration from baseline to primary vitrectomy; number of intraocular procedures required; BCVA; grade of vitreous hemorrhage at 6 weeks; and grading of lens clarity using LOCS II. Safety outcomes included all adverse events (AEs) and serious adverse events (SAEs). All AEs and SAEs were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, version 19.0. Intraoperative surgical complications were also prospectively recorded.
Summary of eligibility criteria	Inclusion criteria included adults (male or female over 18 years) with Type 1 or Type 2 diabetes mellitus with a Grade 2 - 4 fundus obscuring vitreous hemorrhage of at least 2 months duration in the study eye. Participants had a best corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity (VA) from 40 letters to perception of light in the study eye. Key exclusion criteria included the presence of any tractional retinal elevation on examination or B-mode ultrasound; patients listed for vitrectomy for solely recurrent, rather than persistent, vitreous hemorrhage; prior intravitreal drug therapy and use of new or changed medications that target hemostasis within 3 months of screening, including antithrombotic, antiplatelet and anticoagulant therapy.
Primary efficacy parameter	Number of participants deemed to require vitrectomy at

	week 7, as assessed at the visit 6 weeks after ranibizumab/placebo. Assessed by: 1) ETDRS Visual Acuity 2) Slit-lamp examination of the anterior segment and biomicroscopy of the fundus 3) B mode ultrasound scan if necessary 4) Vitreous haemorrhage grading
IMP	Ranibizumab 0.05 mL (Lucentis, Novartis, Frimley, UK)
Dosing regimen	At baseline a single intravitreal injection of 0.5 mg of ranibizumab in 0.05 mL (Lucentis, Novartis, Frimley, UK) was administered to participants in the treatment group. Placebo treatment comprised a single subconjunctival injection of 0.05 mL of 0.9% sodium chloride (Noridem Enterprises Ltd, Wellingborough, Northamptonshire, UK).
Sample size	24
No. participants recruited	24
No. withdrawals	2
No. participants completing study	22
SAEs reported	A total of 41 SAEs were reported, of which 22 were in the IMP group and 19 were in the placebo group
IMP Dosing and recoded adverse events / important medical events	There were two deaths in the placebo group, and both deaths had a vascular cause as per APTC criteria. None of the non-study eye or non-ocular AEs or SAEs were considered to be related to ranibizumab or vitrectomy.
Protocol deviations	Kings = 10 GSTT = 7
Reason for early termination	N/A
Conclusions	**Results:** Eight out of 12 participants (66.7%) in the ranibizumab group required vitrectomy at week 7 versus 12 out of 12 (100%) in the placebo group (absolute risk reduction 33.3%, 95% confidence interval 2.1% to 70.7% [Newcombe-Wilson]; p = 0.09 [Fisher's exact test]). One additional eye in the ranibizumab group required vitrectomy by 12 months. The mean (± 1 standard deviation) grade of vitreous hemorrhage at week 6 was 2.7 ± 1.2 in the ranibizumab group and 3.2 ± 0.8 in the placebo group. The mean BCVA at 12 months was 72.7

	± 12.3 letters in the ranibizumab group and 75.1 ± 10.1 letters in the placebo group. The mean duration from baseline to vitrectomy was 12.1 ± 16.0 weeks in the ranibizumab group and 7.3 ± 1.1 weeks in the placebo group. The mean number of intraocular procedures required after baseline ranibizumab/placebo, including any surgery or intravitreal injections, was 1.1 ± 0.3 in the ranibizumab group and 1.1 ± 0.9 in the placebo group. Safety was similar across groups, with no unexpected safety events. **Conclusion and Relevance**: Intravitreal ranibizumab may reduce the likelihood of proceeding to planned vitrectomy in patients with persistent, dense diabetic vitreous hemorrhage. Further studies appear justified.

Timothy Jackson, Chief Investigator

SIGNATURE: _____

DATE: 29 Aug 17