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Electronic Retinal Prosthesis for Severe Loss of Vision in Geographic Atrophy in Age-Related Macular Degeneration: First-in-Human Use

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Keywords:	RETINA, Age-Related Macular Degeneration < RETINA, Macular and RPE Dystrophies < RETINA, Inner retinal/Vitreoretinal dystrophies < RETINA, Retinal Pathology / Research < RETINA, Retinitis Pigmentosa < RETINA, Pars Plana Vitrectomy < VITREOUS / ENDOPHTHALMITIS
Abstract:	<p>BACKGROUND: To date there are yet no available approved therapies for Geographic Atrophy (GA) secondary to age-related macular degeneration (AMD).</p> <p>METHODS: Single site, non-randomized safety and efficacy study presenting the preliminary results in a cohort of five late stage AMD (GA) patients successfully implanted with the Argus II Retinal Prosthesis System (Second Sight Medical Products Inc., Sylmar, California, USA). Extensive fundus imaging including retinal photographs from which the GA area was measured. A combination of custom and traditional tests designed for very low vision subjects assessed visual function in study subjects. A Functional Low-Vision Observer Rated Assessment was</p>

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	<p>carried out to evaluate the impact of the system on the subject's daily life. In addition, a study to evaluate structural characteristics of the visual cortex of the brain was performed in one subject using magnetic resonance imaging.</p> <p>RESULTS: 7 device-related adverse events were reported, 4 of which were classed as serious adverse events. Retinal detachment was reported in 3 patients and was successfully treated within 12 months of onset. Testing showed an improvement in visual function in 3 of 5 patients with the system turned on. Magnetic resonance imaging assessed in one patient after implantation indicates a selective increase in cortical myelin and thickness in visual brain regions one year post implantation.</p> <p>CONCLUSIONS: Epiretinal prostheses can successfully be implanted in those affected by GA secondary to late-stage AMD and can elicit visual percepts by electrical stimulation of residual neuroretinal elements and improve basic visual function in those affected.</p>

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4 1 **Electronic Retinal Prosthesis for Severe Loss of Vision in Geographic**
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6 2 **Atrophy in Age-Related Macular Degeneration: First-in-Human Use**
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60 25 This article contains additional material: S1 Fig and S1 Table.

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3 26 Trial registration number on ClinicalTrials.gov: NCT02227498
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6 27 **Short title:**

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8 28 Electronic retinal prosthesis trial in GA-AMD
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13
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15
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17
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Abstract

BACKGROUND: To date there are yet no available approved therapies for Geographic Atrophy (GA) secondary to age-related macular degeneration (AMD).

METHODS: Single site, non-randomized safety and efficacy study presenting the preliminary results in a cohort of five late stage AMD (GA) patients successfully implanted with the Argus II Retinal Prosthesis System (Second Sight Medical Products Inc., Sylmar, California, USA). Extensive fundus imaging including retinal photographs from which the GA area was measured. A combination of custom and traditional tests designed for very low vision subjects assessed visual function in study subjects. A Functional Low-Vision Observer Rated Assessment was carried out to evaluate the impact of the system on the subject's daily life. In addition, a study to evaluate structural characteristics of the visual cortex of the brain was performed in one subject using magnetic resonance imaging.

RESULTS: 7 device-related adverse events were reported, 4 of which were classed as serious adverse events. Retinal detachment was reported in 3 patients and was successfully treated within 12 months of onset. Testing showed an improvement in visual function in 3 of 5 patients with the system turned on. Magnetic resonance imaging assessed in one patient after implantation indicates a selective increase in cortical myelin and thickness in visual brain regions one year post implantation.

CONCLUSIONS: Epiretinal prostheses can successfully be implanted in those affected by GA secondary to late-stage AMD and can elicit visual percepts by electrical stimulation of residual neuroretinal elements and improve basic visual function in those affected.

60 Introduction

61 Almost 1 in 25 people worldwide suffer from severe visual impairment, in the form of
62 low vision or blindness [1]. In a significant proportion, approximately 10 to 20%, visual
63 impairment is irreversible. As a result, vision regeneration has recently become the focus of
64 some exceptional research in an attempt to restore some of the lost vision. Several different
65 approaches have been investigated to restore sight to those suffering from severe visual
66 impairment due to retinal or neurological degenerations, including gene therapy and visual
67 prostheses [2-10]. Age-related Macular Degeneration (AMD) is a disease which describes a
68 broad designation of signs and symptoms which can significantly impact the retina and
69 consequent vision. Early and intermediate AMD are characterised by the presence and size of
70 soft drusen, comprising of lipid deposits at the level of the retinal pigment epithelium (RPE).
71 Late AMD describes the loss of central vision as a result of damage to the macula and can be
72 sub-categorised into two forms: Neovascular AMD and Geographic Atrophy (GA). The latter
73 is characterised by chronic and currently irreversible atrophy affecting the RPE and
74 photoreceptor cells, resulting in a progressive and devastating loss of vision[11]. It is
75 estimated that 30-50 million people are affected by AMD globally and this is likely to
76 increase with the aging population. It is estimated that by 2040 the number affected by late
77 AMD is set to double, and while those with the Neovascular type can receive treatment in the
78 form of Anti- Vascular Endothelial Growth Factor (Anti-VEGF), there is no treatment for
79 those affected by GA currently [12,13].

80 Humayun et al showed that intraocular direct electronic stimulation of atrophic retina
81 in AMD using a probe during pars plana vitrectomy surgery can elicit visual phosphenes for
82 the duration of the probe-retina contact [14]. The aim of the retinal prosthesis is to elicit
83 neural activity in the remaining retinal neurons by detecting light and converting it into
84 electrical stimuli using artificial devices. As mentioned above, in GA the outer retinal

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3 85 structures and photoreceptor cells become depleted whereas inner retinal structures are left
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5 86 partially intact and therefore can elicit some visual potential [15]. The Argus® II Retinal
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7 87 Prosthesis System (Second Sight Medical Products Inc., Sylmar, California, USA) is a
8
9 88 commercially available device that aims to restore a basic level of vision to patients with
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11 89 profound vision loss from outer retinal dystrophies [16].
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13

14 90 Since obtaining a CE mark in 2011 and FDA approval as a humanitarian device in
15
16 91 2013, the device has been predominantly utilised for patients with total loss of vision from
17
18 92 rare genetic diseases such as retinitis pigmentosa (RP) and choroideremia [14,16-24]. AMD
19
20 93 remains one of the leading causes of registered legal severe visual impairment and
21
22 94 irreversible blindness among the elderly in developed parts of the world [25]. Unlike RP or
23
24 95 choroideremia, AMD primarily affects the central retina, which is responsible for high
25
26 96 resolution vision necessary for reading, driving as well as face and object recognition.
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28 97 Patients do maintain their peripheral vision; however, this does not allow the completion of
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30 98 the aforementioned tasks. Constant use of peripheral vision is also extremely taxing on the
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32 99 patient as they are constantly trying to change their angle of vision by moving their heads and
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34 100 eyes.
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40 101 Here we describe preliminary safety and efficacy results of five patients with a
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42 102 diagnosis of advanced GA in late-stage AMD implanted with the Argus® II Retinal
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44 103 Prosthesis System.
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49 105 **Methods**

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52 106 The study conformed to World Medical Assembly Declaration of Helsinki 1964 and
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54 107 subsequent revisions. The study was conducted with compliance to the spirit of Good Clinical
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56 108 Practice and appropriate approvals were granted from the Human Research Authority (HRA)
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58 109 and the study was approved by Medicines and Health Products Regulatory Agency (MHRA)
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3 110 in the UK and the North West Greater Manchester Research Ethics Committee. The study
4
5 111 was registered on www.clinicaltrials.gov, trial registration number NCT02227498. Written
6
7 112 information was provided to all participants in clear, written form to aid verbal explanations
8
9
10 113 given by the study team. Audio versions of study documents were also prepared and used
11
12 114 where applicable. Written informed consent was obtained prior to enrolment of each
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14
15 115 participant enrolled on to the study.

18 116 **Trial design**

21 117 This is a single arm, non-randomised, controlled feasibility study at a single site.
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23 118 Potential candidates were screened to ensure they were eligible for the study until the
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25 119 recruitment target of 5 patients was achieved. The first participant was consented on January
26
27
28 120 2015 but did not meet the inclusion criteria. The first included participant was consented on
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30 121 April 2015 and the fifth and last included participant was consented on January 2016. To
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32 122 date, the follow-up time ranges from 24 to 36 months approximately. Fig 1 shows the
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34
35 123 CONSORT flow diagram with further details on screening fails and enrolled participants.

37 124 **Fig 1. CONSORT Flow Diagram.** Progress shown through the phases of the trial
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39 125 (enrolment, intervention allocation, follow-up, and data analysis) up to the first 12 months
40
41 126 reported in the present manuscript.

44 127 The inclusion criteria were: subjects aged between 25 and 85 years of age who
45
46 128 consented to participate in the study; a diagnosis of late-stage AMD (i.e., evidence of drusen
47
48 129 and hyperplasia of the RPE in the eye with GA secondary to late-stage AMD as determined
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50
51 130 by the investigator); severe sight impairment meeting the following additional criteria:

- 53 131 • Visual acuity of logMAR 1.0 (6/60) or worse in both eyes as measured by ETDRS;
- 55 132 • Hand motion or worse central vision in the eye to be implanted, as measured with a
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57 133 pinhole occluder;

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3 134 • GA (confirmed by Fundus Autofluorescence) of at least 18 mm² extent and central
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5 135 scotoma (confirmed by microperimetry) in the central 20° or more.
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8 136 • In cases of bilateral GA that meet the study criteria, the eye with worse vision (per
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10 137 ETDRS VA and microperimetry results) will be chosen for the study procedure.
11

12 138 Additionally, subjects had to be pseudophakic with an IOL successfully implanted in
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15 139 the study eye at least 2 weeks before baseline testing, or aphakic with a clear capsule;
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17 140 subjects had to be both motivated and competent to learn to use the Argus II System (by the
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19 141 Investigator's assessment), and willing and able to commit to the study requirements
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21 142 (including an understanding of the requirements of the study and acceptance of the time
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23 143 involved in participating). Finally, subjects included in the study must not be suffering from
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26 144 non-ophthalmic serious adverse events (e.g., myocardial infarction, etc.) or from non-curable
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28 145 life-threatening conditions (e.g. cancer) at the time of the Baseline visit.
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31 146 Criteria for exclusion of the trial were ocular diseases or conditions that could prevent
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33 147 the Argus II implant from working (e.g., optic nerve disease, central retinal artery or vein
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35 148 occlusion, history of retinal detachment, trauma, etc.); ocular structures or conditions that
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38 149 could prevent the successful implantation of the Argus II Implant or adequate healing from
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40 150 surgery (e.g. extremely thin conjunctiva; axial length <20.5 mm or > 26 mm; corneal ulcers;
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42 151 abnormalities in the typical curvature of the retina like staphyloma and all causes of
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45 152 significant protrusions or depressions at the macular that could compromise the optimal
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47 153 position of the electrode array, active or severe blepharitis, evidence of active sub-macular
48
49 154 choroidal neovascularization (CNV) in proposed study eye etc.); ocular diseases or conditions
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51 155 (other than cataracts) that prevent adequate visualization of the inner structures of the eye
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54 156 (e.g., corneal opacity). Also excluded from the trial were those subjects with an Implantable
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56 157 Miniature Telescope in either eye; pre-disposition to eye rubbing or with any disease or
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3 158 condition that prevents understanding or communication of informed consent, study
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5 159 demands, and testing protocols, including:

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8 160 • Cognitive decline including diagnosed forms of dementia and/or progressive
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10 161 neurologic disease,
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12 162 • Psychiatric disease including diagnosed forms of depression;
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14 163 • Does not speak a principal language associated with the region, and
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17 164 • Deafness or selective frequency hearing loss that prevents hearing device alarms and
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19 165 alerts.

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21 166 Additional reasons for exclusion were subjects being pregnant or wishing to become
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23 167 pregnant during the course of the study; participating in another investigational drug or
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25 168 device study that may conflict with the objectives, follow-up or testing of this study; subjects
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27 169 with inability to tolerate general anaesthesia or the recommended antibiotic and steroid
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29 170 regimen associated with the implantation surgery and those subjects with conditions likely to
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31 171 limit life to less than 1 year from the time of inclusion.

32
33 172 [A full list of inclusion/exclusion criteria is also recorded at www.clinicaltrials.gov, trial
34
35 173 registration number NCT02227498]

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37 174 While not a specific exclusion criterion, patients with Stargardt's or other hereditary
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39 175 macular degenerations were not included in this trial. They were excluded on the basis of not
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41 176 meeting the primary inclusion criterion of being diagnosed with late-stage AMD (GA). This
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43 177 determination was made by the investigator after review of the medical history, fundus
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45 178 imaging, and other screening assessments.

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47 179 Each of the recruited patients, accompanied by at least one family member, had a
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49 180 thorough consultation with our research team to understand the nature of this study and set
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51 181 realistic expectations. All patients gave their written informed consent and the study adhered
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53 182 to the Declaration of Helsinki. The study was approved by Medicines and Health Products
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3 183 Regulatory Agency (MHRA) in the UK and the North West Greater Manchester Research
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5 184 Ethics Committee. Study procedures carried out to ensure eligibility for the study and to
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8 185 monitor structural and functional changes included the following: optical coherence
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10 186 tomography (OCT), wide-field retinal fundus photography, fundus autofluorescence and
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12 187 fluorescein angiography by means of the OPTOS California (Optomap; Optos PLC.,
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14 188 Dunfermline, Scotland, United Kingdom), visual field assessed by the Humphrey Field
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16 189 Analyzer (HFA; Carl Zeiss Meditec Inc., Dublin, CA), testing with modified visual acuity
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18 190 (VA) tests for extremely low vision subjects (described elsewhere [17,19,21]) and completion
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20 191 of the Functional Low-Vision Observer Rated Assessment (FLORA) [26,27].
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24 192 **Surgery**

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27 193 The Argus II System consists of two main components: an extra- and intraocular
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29 194 portion and an external unit worn by the user (Fig 2).
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31 195 **Fig 2. Argus II System.** The implant consists of a receiving coil for receiving information
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33 196 and power from the external components of the Argus II System, an electronics package that
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35 197 is secured to the outside of the eyeball using a standard scleral band and that drives
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37 198 stimulation of the electrodes and an electrode array (60 electrodes arranged in a 6 x 10 grid)
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39 199 that is secured to the surface of the retina by a retinal tack (upper row). The implant receives
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41 200 power and data commands wirelessly from an external unit. The externals are composed of
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43 201 the Argus II Glasses and the Argus II Video Processing Unit (VPU) (lower row). A small,
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45 202 light-weight video camera and a transmitting coil are mounted on a pair of glasses. The
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47 203 glasses are connected to the VPU via a cable. The VPU is worn by the subject and it converts
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49 204 the video image captured by the video camera into stimulation commands. The telemetry
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51 205 coils and radio-frequency system are mounted on the ear piece for transmitting data from the
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53 206 VPU to the implant. The implant is provided in both left and right eye configurations. The
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3 207 device is only implanted in one eye. The study eye was decided according to the requirements
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5 208 set up in the inclusion criteria.
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8 209 The extraocular portion of the implant was inserted under the extraocular muscles.
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10 210 The implant was fixed to the eye via sutures passed through suture tabs on the implant and
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12 211 secured by a scleral band. In order to insert the intraocular portion implant, core and
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14 212 peripheral vitrectomies were performed, followed by dissection of any epiretinal membrane
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16 213 in the area where the electrode array would be placed. The electrode array was then inserted
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18 214 through an opening in the temporal part of the sclera and secured onto the retina using a
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20 215 retinal tack. Extensive training and support was provided by the study sponsor for the
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22 216 surgical staff involved with the study. Professor Stanga had prior experience with the surgical
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24 217 technique described above from the previous RP study at MREH.
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28 **Study assessments**

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31 219 The safety endpoints for this study were the number and nature of adverse events (AEs) in the
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33 220 implanted subjects. AEs and Serious Adverse Events (SAEs) were documented throughout
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35 221 the study and included in the data analysis for safety evaluation.
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39 222 Visual function was assessed for all implanted subjects between both the implanted
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41 223 and fellow eye, providing data on natural course. Study specific training and certification was
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43 224 provided by Second Sight to ensure that all involved staff were appropriately trained for their
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45 225 role on the study. Visual function testing was carried out by specific research optometrists
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47 226 and assistants named on the study delegation log. ETDRS Visual Acuity (VA), Grating VA,
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49 227 Square Localisation and Direction of Motion tests comprised the visual function tests.
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52 228 Grating VA, Square Localisation and Direction of Motion tests were custom designed
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54 229 and provided by Second Sight. Monocular visual acuity (VA) was assessed using ETDRS
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56 230 Visual Acuity and Grating VA methods with the system turned On/Off in the study eye.
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3 231 Traditional methods were used to assess ETDRS VA; central VA measured at 3 meters using
4
5 232 the appropriate 3-meter chart. If a score worse than 1.0 logMAR was obtained the test was
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7 233 repeated at 1 meter. Grating VA was necessary in those with a visual acuity between 1.6 and
8
9 234 2.9 logMAR.
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12 235 Binocular VA was assessed using Square Localisation and Direction of Motion, assessing
13
14 236 basic visual function in addition to traditional methods of VA assessment. Square
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16 237 Localisation assessed the subject's ability to determine light localisation by assessing how
17
18 238 well the subject could distinguish a white square of varying size against a black background.
19
20 239 Direction of Motion assessed motion discrimination by having the subject draw the same
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22 240 direction of a horizontal line presented to them via a touchscreen monitor.
23
24 241 For visual function assessments the subjects served in three ways as their own control:
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26 242 comparisons are performed between the system turned ON and OFF, between implanted eyes
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28 243 and fellow eyes, and between pre-surgery and post-surgery performance. When results were
29
30 244 compared with the camera ON and OFF and both eyes open, data from a particular subject at
31
32 245 a particular time point was analysed with a two-tailed t-test assuming unequal variances.
33
34 246 Visual function testing was performed at the baseline visit, 3, 6 and 12 months post-op.
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36 247 A quality of life questionnaire (QOL) was also performed by each patient with the system
37
38 248 turned ON and OFF. The impact of the system on the patients' daily life was rated by expert
39
40 249 observers in the Functional Low-Vision Observer Rated Assessment (FLORA) QOL
41
42 250 questionnaire. FLORA scores on observed functional vision tasks range from 4 (impossible)
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44 251 to 1 (easy).
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253 **Cortical changes**

254 An additional research study was carried out in conjunction with the Argus II
255 feasibility clinical trial to assess the visual cortex of the brain before and after implantation of
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2
3 256 the retinal prosthesis. This part of the study was approved by the NHS Health Research
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5 257 Authority (IRAS reference 171426; <http://www.isrctn.com/ISRCTN52484108>) and the York
6
7
8 258 Neuroimaging Centre Research and Governance Committee. Informed written consent was
9
10 259 obtained from all participants, adhering to the Declaration of Helsinki. Magnetic resonance
11
12 260 imaging (MRI) was used to assess two structural characteristics in the cerebral cortex (grey
13
14 261 matter) of the brain: cortical thickness and cortical myelin levels. Three of the five patients
15
16 262 (patients # 133, # 547 and # 628) were scanned 5-19 days before implantation with the
17
18 263 epiretinal prosthesis. Post-implantation assessments were carried out 13 months following
19
20 264 surgery in patient # 628. Of the remaining two patients scanned pre-implantation, one was
21
22 265 deceased and one withdrew for non-study related reasons. Eight sighted, age-matched control
23
24 266 participants (4 females, mean age 75.1 years, age range 70-83 years) were also scanned under
25
26 267 the same MRI protocol that generated 3D models of the cortical surface [28]. Post-
27
28 268 implantation MRI adhered to published safety guidelines on MRI use with the implant device
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30
31 269 turned OFF [29].

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35 270 Mean cortical thickness and mean cortical myelin levels were measured in three
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37 271 regions of interest [28] before and after implantation: V1 (primary visual cortex), V2
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39 272 (secondary visual cortex) and a non-visual control region, OP2, an area in the parietal
40
41 273 operculum that has thickness and myelination levels to visual cortex.
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46 47 275 **Results**

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49
50 276 We successfully recruited 5 eyes with a diagnosis of late-stage AMD (GA) but no
51
52 277 other comorbidity that could affect their vision. Three female and two male patients had the
53
54 278 Argus II System successfully implanted in one eye (i.e. 3 right (OD) and 2 left (OS)). The
55
56 279 mean age of recruited patients was 75 years (± 4.6 , range: 70.7–79.9). Due to the (non study-
57
58 280 related) death of one participant four months after recruitment, surgical results include data

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3 281 from 5 participants, but visual function and functional vision results include data from up to
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5 282 four participants. This study presents the initial results following the first 12 months of the
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7 283 study, of which continued for a further 4 years approximately.
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10 284 **Surgical and safety results**

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13 285 During the implantation surgery there were no complications and surgical results are
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15 286 considered reproducible across the 5 implanted eyes. All 5 implants were placed over the
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17 287 centre of the retina (i.e. macula), where structural and functional defects, that is atrophic
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19 288 retinal areas and central scotomas, were identified and correlated. In 3 of the 5 occasions the
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21 289 visible atrophic central area was smaller than the retinal area covered or very nearly covered
22
23 290 by the implant electrodes. Adverse Events (AEs) and Serious Adverse Events (SAEs) were
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25 291 documented throughout the study. During the first 12 months of follow up, we recorded 7
26
27 292 study-related AEs of which 4 were classified as SAEs related to the procedure or device. The
28
29 293 SAEs were: one localised non-rhegmatogenous retinal detachment (RD) under the cable
30
31 294 (Study ID #214), two cases of proliferative vitreoretinopathy (PVR)/retinal detachment
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33 295 (Study IDs #547, #950, and one case of hypotony (Study ID #628).
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38 296 All SAEs responded to gas injection or pars plana vitrectomy surgery with silicon oil
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40 297 and were all resolved within 1 year of onset. One patient also required retinectomy. In
41
42 298 addition, a scleral patch graft was placed in the subject suffering from hypotony to prevent
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44 299 the leakage around the entry site of the cable.
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47 300 The localized non-rhegmatogenous RD under the cable was observed 1 day after the
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49 301 implantation surgery and may have been induced during a first unsuccessful attempt of array
50
51 302 insertion into the vitreous cavity. Prior to array insertion there may have been a non-full
52
53 303 thickness choroidal cut at the ends of the 5.2mm incision causing the array to push against the
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55 304 choroid. After this first unsuccessful attempt of array insertion the surgeon ensured a full-
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3 305 thickness, full-width choroidal cut with a 15° Stab Knife and Hoskins Forceps. The second
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5 306 attempt of array insertion was uneventful. The RD was treated with gas injection.
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8 307 The two cases of PVR/retinal detachment with a total tractional retinal detachment in
9
10 308 the 4 quadrants were observed 1.4 months post-implant and 1.9 months post-implant,
11
12 309 respectively. The events were treated with a pars plana vitrectomy, membrane peeling and
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14 310 silicone oil injection. Both patients reported a loss of peripheral vision in the implanted eye
15
16 311 that recovered after this treatment. In both cases the artificial perception was not affected by
17
18 312 the PVR/retinal detachment.
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21 313 A non-serious and stable macular oedema (MO) was observed in all patients from
22
23 314 approximately 1 month after implantation and during the course of the follow-up (Fig 3). The
24
25 315 macular oedemas were not treated because they did not have any impact on the artificial
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27 316 perception elicited by the retinal prosthesis.
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31 317 **Fig 3. Retinal Fundus and Autofluorescence Images at 1 month.** Right eye shown with
32
33 318 large atrophic macular area (upper left) and Left eye shown with a small atrophic area (lower
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35 319 left). The implant has been placed over the atrophic region. OCT scans from the same eyes
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37 320 show examples of the Macular Oedemas observed in all eyes.
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40 321 A summary of AEs is given in S1 Table, although further and more specific details on
41
42 322 non-serious AEs are beyond the scope of this report.
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45 323 **Electrical Stimulation Results**

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47 324 Pre-implantation baseline tests revealed no signs of visual function over the affected
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49 325 atrophic area of central retina (S1 Fig). Post-implantation, all subjects reported perceiving
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51 326 phosphenes in response to electrical stimulation from electrodes over the atrophic areas, both
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53 327 during direct stimulation by the computer, and during stimulation driven by the real-time
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55 328 video image. Moreover, central visual phosphenes continued to be reported following the
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57 329 resolution of AEs.
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3 330 Active AEs in one of the participants (inability of the patient to attend the protocol
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5 331 visit and the testing session), and the death of another (unrelated to the implant), resulted in
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7 332 only three patients participating in visual function assessments. Moreover, missed visits and
8
9 333 errors in the test administration and capture of data resulted in incomplete functional and
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11 334 structural data collection in the three participants (e.g., missing baseline data in patient #133).

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14 335 In the object localization task, in which the patient was required to locate a white
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16 336 square on a black touchscreen with both eyes open, one patient (# 133) showed significant
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18 337 improvement in performance with the system ON compared to OFF at two follow-up visits
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20 338 (Fig 4), though the mean error was higher than that seen at 3 months for both ON and OFF
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22 339 conditions.

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26 340 **Fig 4. Square Localization and Direction of Motion Results.** Individual results of the
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28 341 performance with system ON (green), system OFF (red) and difference (system OFF- system
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30 342 ON, blue) for square localization and direction of motion tests over time for three of the
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32 343 patients. The excluded participant did not have sufficient data to monitor performance over
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34 344 time due to active AEs. The dotted black line is drawn for reference. Values of the difference
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36 345 (system OFF- system ON) above the reference line indicate improved performance with
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38 346 system ON. Axis labels with an asterisk indicate statistically significant differences ($p < 0.05$)
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40 347 in performance with the System ON versus OFF.

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44 348 In a visual motion task, in which the patient was asked to draw the direction of motion
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46 349 of a white line moving across a black screen with both eyes open, performance was
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48 350 significantly better with the system ON in two of the patients (# 214 and # 950) at one visit
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50 351 each. The remaining follow up visits and patients, including all assessments of acuity as
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52 352 measured by Grating Visual Acuity, which is performed monocularly, did not show a
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54 353 significant difference in performance with the system ON and OFF.

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3 354 In contrast to artificial, lab-based visual tasks, usage of the system after one year post-
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5 355 implantation for functional vision in a “real world” environment (Fig 5) was also evaluated.
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8 356 Four subjects participated in the FLORA at baseline and 12 months post-implant. The impact
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10 357 of the system on the patients’ daily life was rated by expert observers in the FLORA as
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12 358 positive for one of the participants and as mildly positive for the remaining three. No
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14 359 instances or reports of double vision, visual confusion, or inability to integrate artificial and
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16 360 residual vision were reported on the case narratives or in anecdotal reports from the patients
17
18 361 or low vision rehabilitation therapist (data not shown). FLORA scores on observed functional
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20 362 vision tasks range from 4 (impossible) to 1 (easy). All FLORA domains improved with the
21
22 363 system ON compared to baseline at one year post-implantation, with the greatest
23
24 364 improvement evident in the visual orientation tasks (Fig 5A). However, all visual task
25
26 365 domains increased in difficulty relative to pre-implantation with the system OFF (Fig 5B).

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30 366 **Fig 5. Results of the Functional Low-Vision Observer Rated Assessment (FLORA).** A)
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32 367 Rating percentages one year after implant activation for the four participants with the system
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34 368 OFF (left column) and ON (right column). B) Average FLORA score differences (N = 4) in
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36 369 two groups (system ON minus OFF at baseline, and System ON minus OFF at 12 months
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38 370 follow-up, respectively) for the different visual task categories. FLORA scores on observed
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40 371 functional vision tasks range from 4 (impossible) to 1 (easy). Difference scores above the OX
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42 372 axis represent better performance with the system ON. Asterisk indicates the only category
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44 373 where system ON performed worse than pre-implantation (interacting with others tasks).

374 **Cortical Changes**

51
52 375 Three-dimensional models of the cortical surface were generated using structural MRI
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54 376 data. Fig 6A shows examples of the 3D cortical surface from the patient, providing
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56 377 qualitative visualisation of cortical thickness and myelin levels across the brain. The three
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3 378 regions of interest (ROI) selected for quantitative measurements are also outlined and
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5 379 labelled – two in visual cortex (V1 and V2) and a third outside of visual cortex (OP2).
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8 380 Quantitative measurements from each ROI are shown in Fig 6B. Prior to implantation
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10 381 with the retinal prosthesis, mean cortical thickness in V1 and V2 in patient # 628 was below
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12 382 that of age-matched controls, but had increased 13 months post-implantation, while thickness
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14 383 in OP2 (the non-visual region) remained close to that of the control group. Cortical
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16 384 myelination levels in V1 also increased in the patient post-implantation, but remained similar
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18 385 to controls in V2, while levels in OP2 decreased slightly, but remained above that of controls.
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21 386 **Fig 6. Cortical Changes.** A) The top two panels are a 3D inflated representation of cerebral
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23 387 cortex of the brain from patient # 628. Left: lateral view; Right: medial view. The top panel
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25 388 represents a cortical myelin map; hot colours (red/yellow/green) indicate highly myelinated
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27 389 areas and colder colours (blue/purple/black) indicate areas with less myelin. The middle
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29 390 panel represents a cortical thickness map (hot colours indicate brain regions with thicker grey
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31 391 matter and colder colours indicate brain regions with thinner grey matter). Three regions of
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33 392 interest representing visual cortex (V1, V2) and a control region (OP2) are outlined in black
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35 393 and indicated with white text/arrows. B) Quantitative structural brain measures from two
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37 394 visual regions (V1, V2) and one nonvisual region (OP2). Left panel: Mean cortical thickness;
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39 395 Right panel: Mean cortical myelin levels. Data shown in red is from patient # 628, pre-
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41 396 surgery, blue bars represent data from the patient post-surgery, and green bars represent
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43 397 averages from a group of age-matched sighted controls (N=8).
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50 51 52 399 **Discussion**

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55 400 This study tested for the first time ever the hypothesis that an electronic epiretinal
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57 401 prosthesis may restore functional vision for patients diagnosed with advanced macular
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59 402 geographic atrophy in late-stage AMD, offering artificial vision in the defective central area
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3 403 of their visual field. This manuscript includes safety and efficacy outcomes and neuro-
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5 404 structural assessments up to the first 12 months after implantation. The reported results show
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7 405 that surgical implantation of an electronic epiretinal prosthesis system is possible in patients
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9 406 with advanced GA, secondary to Late AMD. The results also show that the implant can
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11 407 elicit visual percepts in areas of GA in late AMD patients. Although it is important to take
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13 408 into consideration that our small sample of patients does not allow for a strong statistical
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15 409 interpretation of the structural and functional assessments pre- and post- operatively, study
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17 410 outcomes strengthen our hypothesis that an epiretinal prosthesis approach may be beneficial
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19 411 for this cohort of patients.
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24 412 In this study we observed 3 retinal detachments (one localised non-rhegmatogenous
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26 413 retinal detachment under the cable and two cases of proliferative vitreoretinopathy/retinal
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28 414 detachment; 3 out of 5 subjects experienced RD) and it represents the major SAE. The
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30 415 percentage of clinical trial subjects with RP implanted with the Argus II Retinal Prosthesis
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32 416 System that experienced RD was 6.7% at 1 year after implantation [16], 6.7% at 3 years [21]
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34 417 and 10.0% at 5 years [30]. The non-rhegmatogenous retinal detachment under the cable
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36 418 observed at post-operative day1 was most probably due to the surgical step of forcing the
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38 419 electrode array through a shorter sclerotomy incision against resistance during the array
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40 420 insertion into the vitreous cavity. To reduce the likelihood of such complication, during the
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42 421 sclerotomy incision, a full-thickness, full-width choroidal cut throughout the entire length of
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44 422 the 5.2mm incision should be made. The root causes of the two cases of proliferative
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46 423 vitreoretinopathy/retinal detachment are unclear. A hypothesis could be that PVR/retinal
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48 424 detachment is due to “chronic chorio-retinal inflammation and/or foreign body reaction” as it
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50 425 has been reported when retinal tacks were initially used for the treatment of retinal
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52 426 detachment [31]. Another hypothesis could be that PVR can originate from the large and
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54 427 traumatic 5.2mm pars-plana incision due to the migration and proliferation of retinal pigment
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3 428 epithelium (RPE) cells. In fact, PVR-related total retinal detachment was also observed when
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5 429 performing excision with translocation of RPE/Bruch's Membrane from the paramacular area
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8 430 to the subfoveal space during the treatment of AMD [32]. PVR may also develop from
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10 431 vitreous residuals or from hyaloid residuals that go into hyper-proliferation. The Argus II
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12 432 Surgeon Manual recommends performing the vitrectomy after the extraocular placement of
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14 433 the device. This may hinder meticulous removal of minute amounts of vitreous and hyaloid
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16 434 membrane because of the presence of the implant around the eye. Accurate removal of
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18 435 peripheral vitreous with scleral depressed vitrectomy is limited by the presence of the
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20 436 electronics case and the implant coil in the supero-temporal and infero-temporal quadrants.
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24 437 Vitrectomy may be performed at the beginning of the procedure and before the
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26 438 extraocular placement of the device. Adjuvant combination therapy in the vitrectomy infusion
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28 439 using 5-fluorouracil (5-FU) and low molecular weight heparin (LMWH) for prevention of
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30 440 PVR may also be considered [33].
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33 441 While serious, the device-related adverse events described above have limited
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35 442 impact on vision in these patients. Baseline visual function was primarily affected by their
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37 443 late-stage AMD and central area of GA prior to implantation, given the level of sight
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39 444 impairment caused. Visual function was mainly assessed through three custom-developed
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41 445 computer-based psychophysical tests with the purpose of specifically assessing a range of
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43 446 low vision as that restored by the retinal implant. These same tests were developed for and
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45 447 have been used in a cohort of patients diagnosed with RP and implanted with the Argus II
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47 448 system [30]. However, visual acuity outcomes are not comparable between studies, due to the
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49 449 persistent and varied visual benefit from this cohort's peripheral residual vision, an element
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51 450 that RP patients lack. The authors believe that the design and implementation of these visual
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53 451 function tests should be further tailored to the needs of GA-AMD patients so that more robust
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55 452 conclusions can be drawn in the future regarding the integration of both the natural peripheral
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3 453 vision and the artificial central vision provided by the system. Nevertheless, based on the data
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5 454 obtained so far, it seems possible that a retinal implant could be beneficial to restore some
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8 455 visual function for future late stage AMD (GA) patients.
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10 456 When FLORA is performed, patients serve as their own control as results are
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12 457 evaluated both with the system ON and OFF. However, it should be pointed out that this is a
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14 458 subjective evaluator-reported assessment and neither the evaluator nor the patient was
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16 459 masked to the operational status of the device when completing the tasks. FLORA outcomes
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18 460 at 12 months after implantation from this study are in good agreement with those found in
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20 461 another published multicentre study (in RP patients) [27]. Our results agree with those of
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22 462 Geruschat et al. in that those tasks related to the use of the system in conditions of maximum
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24 463 light contrast such as the visual orientation tasks, appeared to benefit most from usage of the
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26 464 system [27]. In the present study, performance in tasks involving mobility and interaction
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28 465 with others also improved with the system. Such tasks may enhance patient independence and
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30 466 social interaction. Subjects' improved ability to perform functional vision tasks with the
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32 467 System ON compared to OFF suggests that some integration of artificial central vision and
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34 468 natural peripheral vision may occur; the absence of reported monocular double vision or
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36 469 confusion in the implanted eye is further evidence that stimulation from the implant is not
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38 470 detrimental to these patients.
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44 471 MRI assessments of the brain pre- and post-implantation evaluated the impact of
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46 472 vision restoration through use of the implant device on the visual cortex. Previous research
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48 473 reports that long-term visual deprivation from AMD results in reduced grey and white matter
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50 474 [34-36]. MRI could therefore identify whether the Argus II device could potentially prevent
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52 475 further cortical reductions or even reverse them by restoring visual input to the brain.
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55 476 Statistical analysis could not be performed, as only one patient (# 628) completed
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57 477 MRI both pre- and post-implantation. Nevertheless, data for this patient showed an increase
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3 478 in cortical thickness following 13 months' use of the device from baseline. This increase was
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5 479 observed in both primary visual cortex (V1), the first cortical region in the brain that receives
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7 480 visual inputs, and in secondary visual cortex (V2), and associative visual area. However, no
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9 481 increase in thickness was observed in a control region of the brain not associated with visual
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11 482 processing (OP2). Therefore, the lack of change observed here could indicate that increases
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13 483 in visual cortex are due to use of the Argus II device, but such a conclusion cannot be made
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15 484 without conducting a large-scale study.
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19 485 Areas with high cortical myelin levels are usually primary sensory or motor in
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21 486 function, reflecting a large proportion of inputs or outputs. In this study, we observed an
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23 487 increase in cortical myelin in the patient in V1 13 months post-implantation, possibly as a
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25 488 result of the restoration of visual input signals from the system. No change was observed in
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27 489 cortical myelin in V2 post-treatment; it is possible such changes might take longer to
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29 490 develop. Whether these reported changes correspond retinotopically to the macula in the
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31 491 implanted eye or to the contralateral eye is yet to be determined. However, the fact that
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33 492 changes were significant enough to affect mean thickness and myelin throughout visual
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35 493 cortex suggests the implant may have a positive effect overall.
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40 494 In summary, the recruitment of five patients with GA-AMD and their implantation
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42 495 with an electronic epiretinal implant has offered a plethora of information over the first 12
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44 496 months and potentially opens doors to more research in this area and future clinical
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46 497 indications for artificial vision. Invaluable data is still being collected from four of those
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48 498 patients giving a great opportunity to the research community to assess whether a retinal
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50 499 prosthesis is a feasible approach for the treatment of GA-AMD, one of the most common eye
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52 500 pathologies responsible for severe visual impairment. The system has proven to be safe and
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54 501 favourable in patients with total vision loss from RP and choroideremia. However, the current
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56 502 implant design, which has gained regulatory approval for implantation in patients with severe
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3 503 outer retinal degeneration and has proven to be beneficial for the above cohort, does not have
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5 504 the same quality of life changing effect on patients with GA secondary to late stage AMD.
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8 505 Nevertheless, we have here shown for the first time ever that an electronic epiretinal
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10 506 implant can elicit visual percepts by electrical stimulation of residual neuroretinal elements
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12 507 over the atrophic macula that can be incorporated by patients into their residual vision with
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14 508 no visual adverse effects such as monocular confusion or double vision.
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16
17 509 It was previously thought that it would be impossible to elicit visual function in
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19 510 atrophic retinal areas with no functional response to focal stimulation by a light stimulus.
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21 511 However, as a result of this study, we strongly believe that further research in this area is now
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23 512 justified and that different approaches in the design of retinal implants themselves (e.g.
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25 513 smaller implant size, larger number of electrodes, redesign of the tack to prevent excessive
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27 514 mechanical forces) and in the image processing software and settings could benefit potential
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29 515 future research candidates.
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33 516 Post 1-year functional results and AEs will be reported in a separate publication.
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35 517 This is the First-in-Human use of artificial vision in patients with residual peripheral vision as
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37 518 well as the first implantation of an electronic retinal prosthesis in GA-AMD. We also show,
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39 519 for the first time, Proof of Concept that an electronic retinal prosthesis can elicit visual
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41 520 percepts by electrical stimulation of residual neuroretinal elements in areas of GA in late
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43 521 AMD patients.
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48 49 523 **Acknowledgments**

50
51
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53
54 525 University of Manchester in 2019 and continues his Clinical, Surgical and R&D activities at
55
56 526 London Vision Clinic, with which he partnered in 2017.
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3 527 Some of the data reported in this manuscript have been presented in scientific
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5 528 ophthalmological meetings, such as the Association of Research for Vision and
6
7 529 Ophthalmology (ARVO), the American Academy of Ophthalmology (AAO) and
8
9 530 EURETINA.

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11
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13
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15
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19
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21
22 536 his clinical, surgical and research activities at the London Vision Clinic, where he is Retina
23
24 537 Lead, Principal Investigator and Partner.

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27
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29
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31
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33
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37
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Supporting information captions

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649 **S1 Fig. Fundus Photographs, OCT, and Microperimetry Results.**

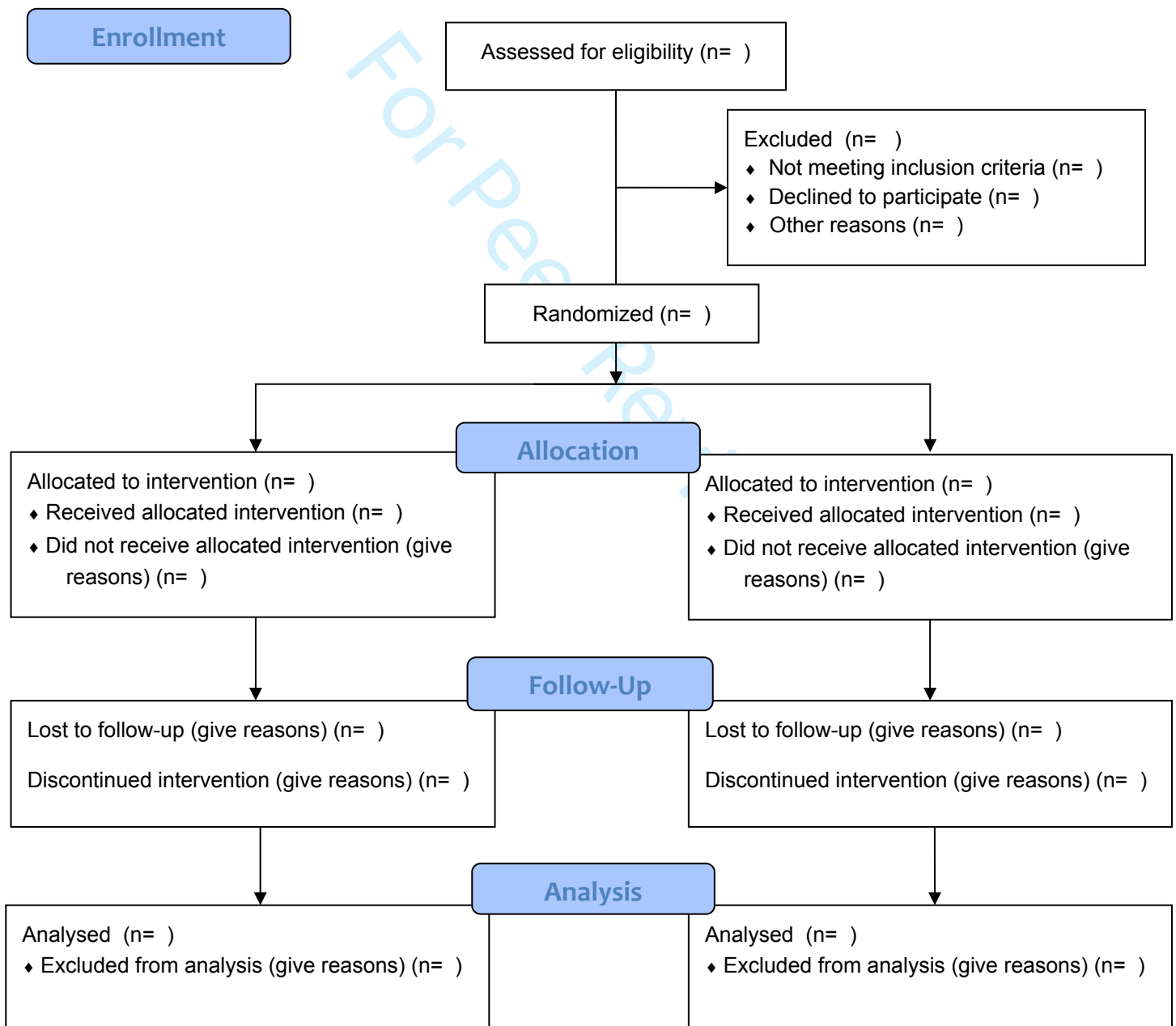
650 **S1 Table. Summary of Adverse Events (AEs).**

For Peer Review



CONSORT 2010 Flow Diagram

****Please note this was a single arm, non-randomised, controlled feasibility study****



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Fig 2

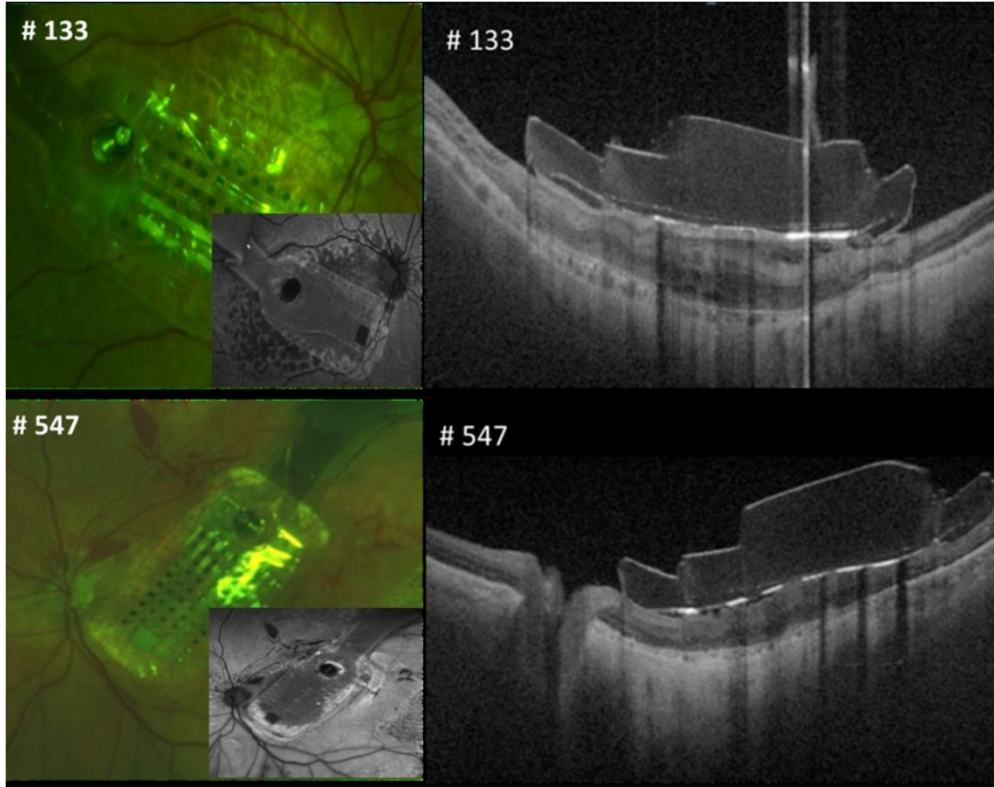


Fig 3

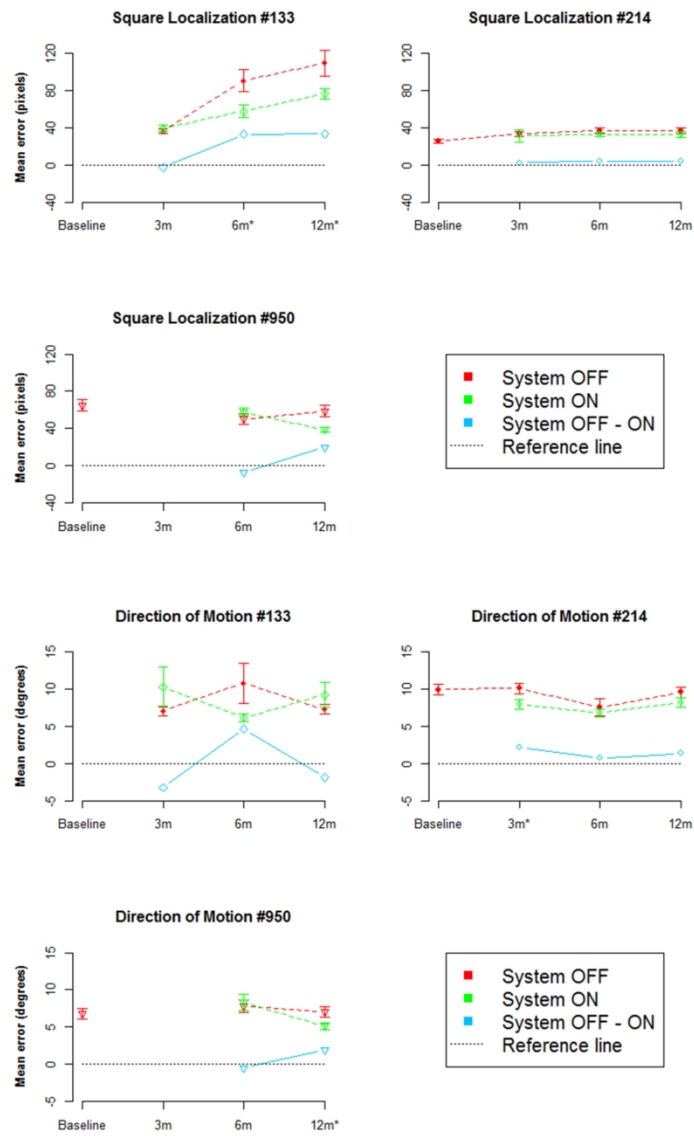


Fig 4

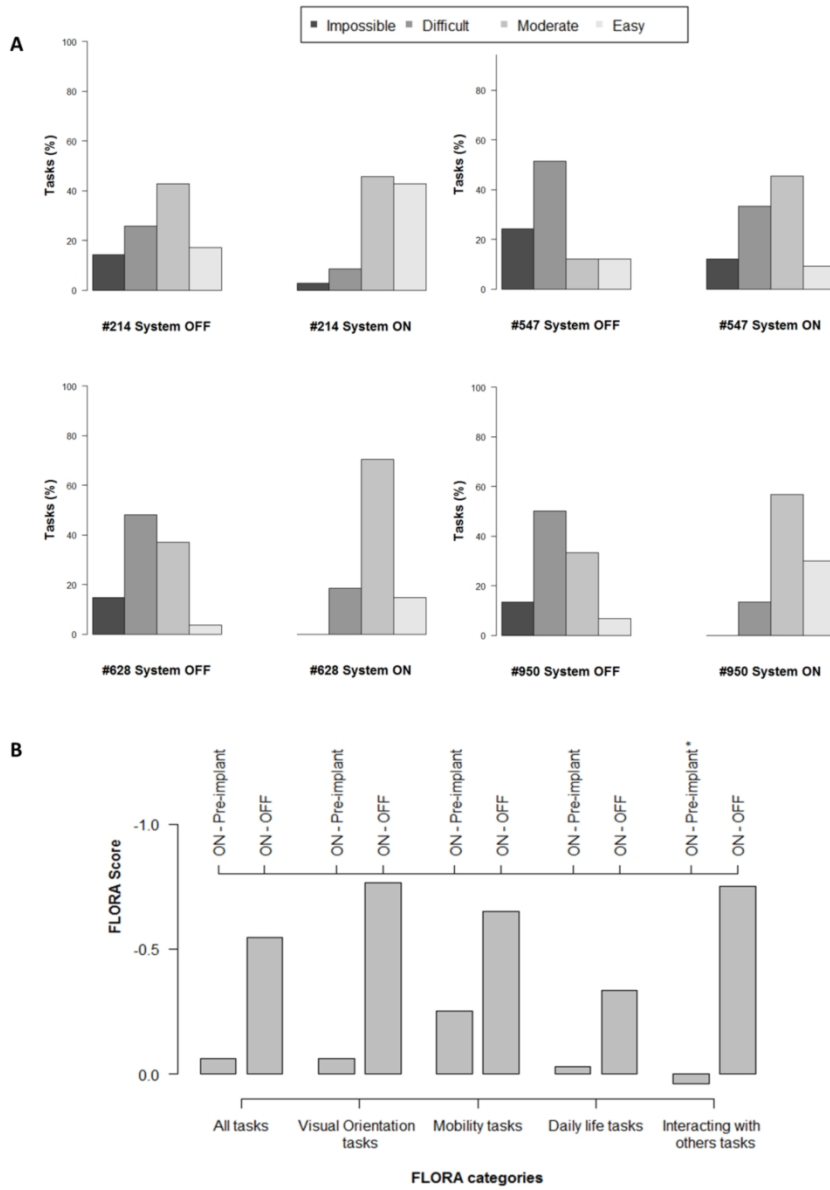


Fig 5

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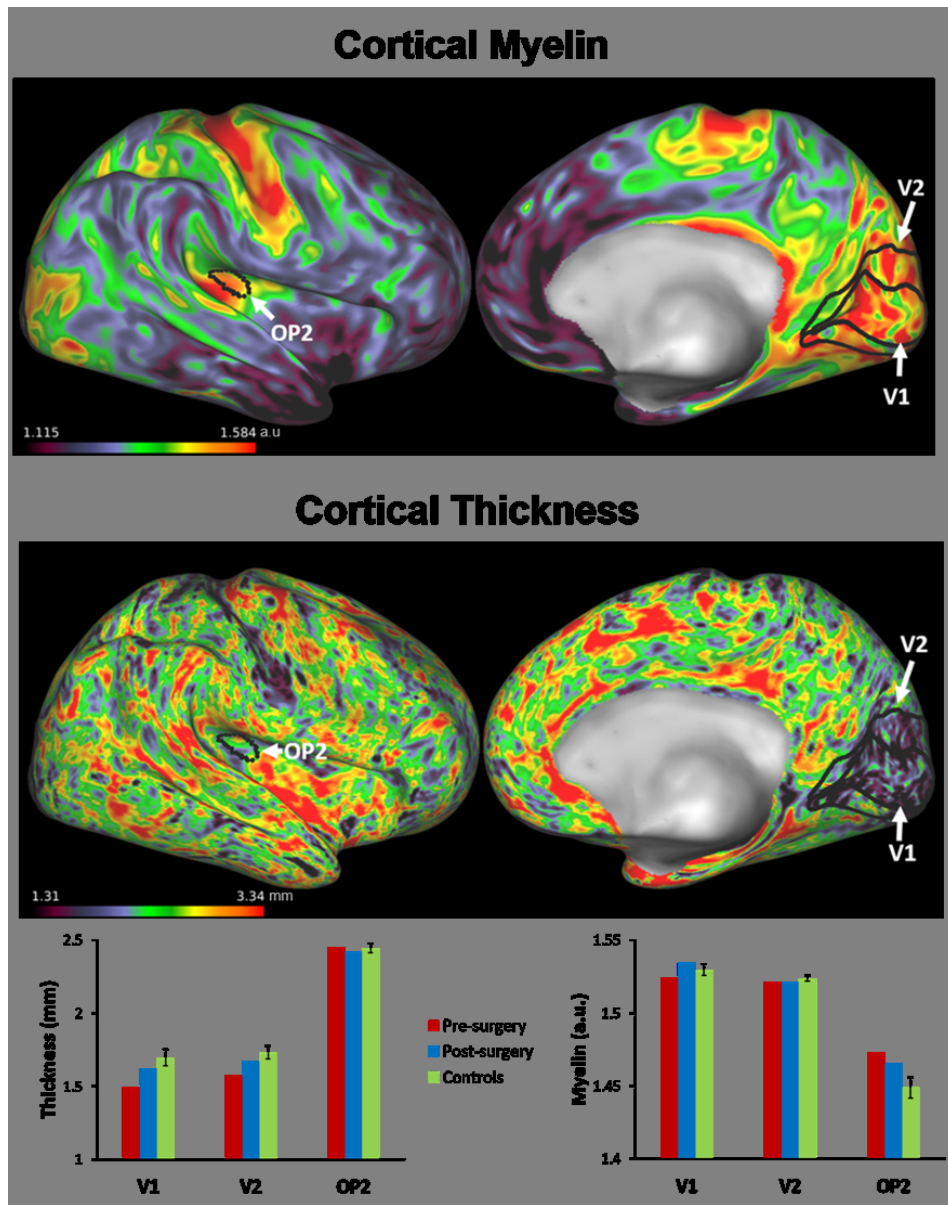
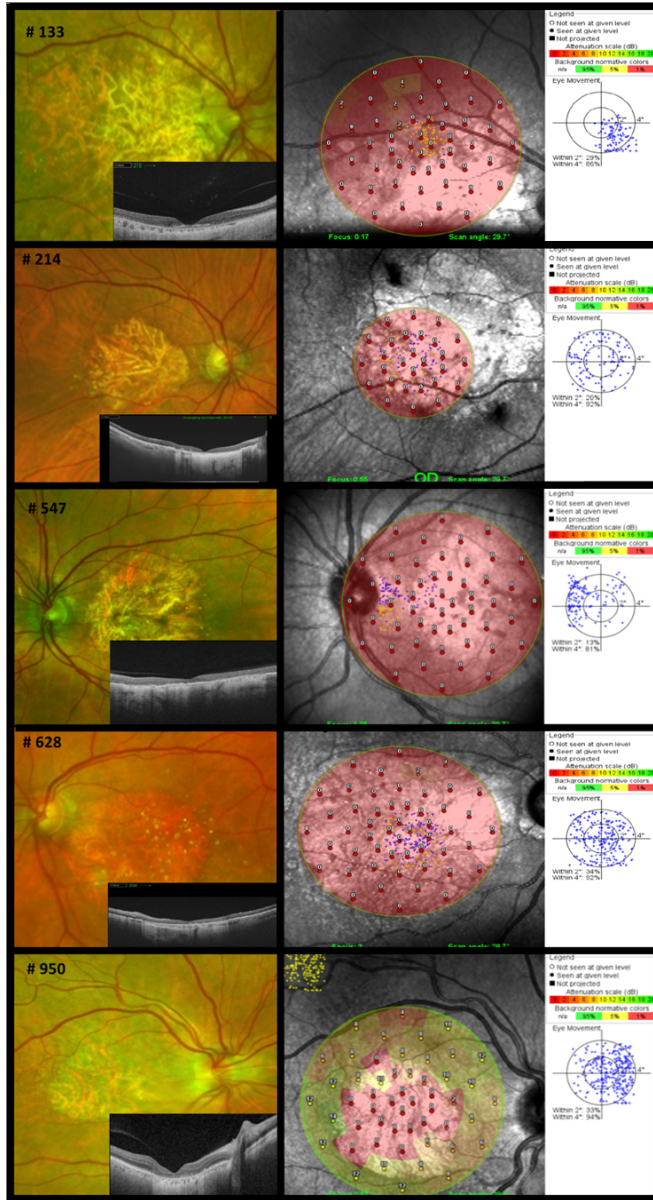


Fig 6

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Study ID	Total Number of SAEs and AEs, study and non-study related	Total Number of study-related AEs	Total Number of study-related SAEs	Brief description of AEs
# 133	0	0	0	
# 214	2	1	1	Light Sensitivity RD
# 547	2	1	1	Floaters PVR Detachment
# 628	2	1	1	Inflammation - ocular Hypotony
# 950	1	0	1	PVR Detachment