Treatment of Leber’s hereditary optic neuropathy: An overview of recent developments

Marta Zuccarelli1,2, Janis Vella-Szijj2, Anthony Serracino-Inglott1,2 and John-Joseph Borg1,3

Abstract
Leber’s hereditary optic neuropathy (LHON) is a rare, maternally-inherited optic neuropathy caused by mitochondrial DNA point mutations and which can cause blindness. Currently, Raxone (idebenone) is the only available medicinal product authorised to treat LHON within the European Union and LHON remains an unmet medical need. The aim of this article was to summarise interventional clinical trials published over the past 5 years (between 2014 and 2019) with the primary purpose of treating LHON. Therapeutic approaches discussed include modulating agents of the mitochondrial electron transport chain such as Raxone, cysteamine bitartrate and KH176, inhibitors of apoptosis such as elamipretide, gene therapy medicinal products such as GS010 and scAAV2P1ND4 and retinal tissue regeneration medicinal products such as bone marrow-derived stem cells.

Keywords
Optic neuropathy, neuro ophthalmology, genetics, hereditary/genetics factors, glaucoma, pharmacology, neuro-ophthalmic disease, paediatric ophthalmology

Introduction
Leber’s Hereditary Optic neuropathy is a rare, maternally-transmitted optic neuropathy caused by point mutations occurring in the mitochondrial deoxyribonucleic acid (mtDNA) which affect mitochondria in retinal ganglion cells (RGCs).1,2 Point mutations m.11778G>A, m.3460G>A and m.14484T>C are the three most prevalent in LHON population, respectively encoding for subunits ND4, ND6 and ND1 of the mitochondrial complex I.3 Due to the mutated genes, an increased production of reactive oxygen species (ROS) occurs leading to a decreased production of ATP and causing apoptosis of RGCs.1 The point mutations m.11778G>A, m.3460G>A and m.14484T>C are also called primary mutations as they cause up to 95% of LHON cases.2,4

LHON is a rare disease with an estimated worldwide prevalence of one in 30,000 for all combined mtDNA mutations. LHON principally affects young adult males.4 Patients carrying one LHON-related mutation can manifest symptoms at any time throughout their lives, with a typical age of onset between second and third decade of life.4 Usually LHON manifests consequentially in the eyes with a rapid and painless onset of loss of central vision in one eye followed by the other eye within days to months.1 Central visual acuity (VA) declines to the level of counting fingers (CF) in most patients.4 With disease progression, individuals usually remain legally blind for the rest of their lives with a permanent large centrocaecal scotoma.1 Cases of spontaneous recovery have been reported and found to be commonly occur with m.14484T>C mutation (37%–58% of cases) but not with mutation m.11778G>A (4% of cases).2,5

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Medicinal products to treat LHON have been studied, but only few of them have been suggested to be effective. Challenges to develop medicinal products to treat LHON are present. Recruitment of naive patients in LHON clinical trials has been reported as a slow process since there are few LHON patients in the EU. Researchers have to consider an added complexity that patients carrying the m.14484T>C point mutation have a 37% to 58% chance of spontaneous recovery of their VA which might introduce biases in the primary end point that are used to study LHON in clinical trials (best recovery in VA determined using the Early Treatment Diabetic Retinopathy Study [ETDRS] charts measured by a logMAR). 

Currently, LHON is an unmet medical need. The aim of this review was to highlight interventional clinical trials that have been published over the past 5 years, between 2014 and 2019, in the international clinical trial databases clinicaltrials.gov and clinicaltrialsregister.eu, with the primary purpose of treating LHON. A prospective treatment protocol has been proposed, including investigational medicinal products retrieved in the international clinical trials databases (Figure 1). Clinical trials have been further discussed in Table 1. Studies that have shown beneficial results in animal experiments have not been discussed.

**Modulating agent of mitochondrial electron transport chain**

A dysfunctional complex I (NADH-ubiquinone oxidoreductase) subunits of the mitochondrial electron transport chain (ETC) is associated with the three most common mtDNA point mutations causing LHON. Affecting complex I, the mutations m.11778G>A, m.14484T>C, m.3460G>A, lead to a deficiency of oxidative phosphorylation (OXPHOS), increased production of ROS and decreased production of ATP, eventually leading to cellular apoptosis.
<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Active substance</th>
<th>Reference</th>
<th>No. of patients</th>
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<th>Main results/preliminary results</th>
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<tr>
<td>Modulating agent of mitochondrial electron transport chain</td>
<td>Idebenone</td>
<td>NCT02774005*</td>
<td>250</td>
<td>12 months</td>
<td>IV</td>
<td>1</td>
<td>(1) Raxone, 900 mg TID</td>
<td>Proportion of eyes with CRR of VA from baseline or in which baseline VA was &gt;1.0 logMAR and was maintained in patients treated with Raxone ≤1 year after the onset of symptoms compared to history control group</td>
</tr>
<tr>
<td></td>
<td>Cysteamine bitartrate</td>
<td>NCT02023866*</td>
<td>36</td>
<td>24 weeks</td>
<td>II</td>
<td>1</td>
<td>(1) Cysteamine bitartrate delayed-release 0.2 to 1.3 g/m²/day BID</td>
<td>Change from baseline in NPMDS sections I to IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT02473445*</td>
<td>22</td>
<td>24 months</td>
<td>II</td>
<td>1</td>
<td>(1) Cysteamine bitartrate delayed-release capsules at a maximum dose of 1.3 g/m²/day, BID</td>
<td>Change from baseline in NPMDS sections I to IV</td>
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<tr>
<td></td>
<td>KH176</td>
<td>NCT02544217*</td>
<td>30</td>
<td>7 days</td>
<td>I</td>
<td>2</td>
<td>(1) Single ascending dose (SAD): single oral dose of 10, 30, 100, 300, 800 and 2000 mg or placebo (2) Multiple ascending dose (MAD): multiple oral doses of 100, 200 and 400 mg were administered BID or placebo</td>
<td>Safety and tolerability (ADRs, routine clinical laboratory, vital signs, electrocardiogram, physical examinations) and pharmacokinetics (peak of plasma concentration, half-life, area under the curve)</td>
</tr>
<tr>
<td>Inhibition of apoptosis</td>
<td>Elamipretide</td>
<td>NCT02693119*</td>
<td>12</td>
<td>56 weeks</td>
<td>II</td>
<td>4</td>
<td>(1) One drop elamipretide 1% topical ophthalmic solution BID in the left eye and one drop of vehicle topical ophthalmic solution (2) One drop elamipretide 1% topical ophthalmic solution BID in the right eye and one drop of vehicle topical ophthalmic solution (3) One drop elamipretide 1% topical ophthalmic solution BID applied to both eyes (4) OLE: one drop elamipretide (MTP-131) 1% topical ophthalmic solution BID applied to both eyes</td>
<td>Incidence and severity of ADRs</td>
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### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Mechanism of action</th>
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<tr>
<td>Gene transference</td>
<td>GS010 (rAVV2-ND4)</td>
<td>NCT02739524*</td>
<td>90</td>
<td>1 year</td>
<td>III</td>
<td>2</td>
<td>(1) Intravitreal injection of GS010 9E10 viral genomes in 90μL balanced salt solution (2) Intravitreal injection of placebo in a volume of 90μL</td>
<td>Change from baseline in the BCVA measured with logMAR at 1-year post-treatment in the eye treated with GS010 and in the eye injected with placebo</td>
<td>No results available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT03153293*</td>
<td>159</td>
<td>12 months</td>
<td>II/III</td>
<td>1</td>
<td>(1) A Single intravitreal injection of recombinant rAAV2-ND4 (0.05 mL) at a dose of $1 \times 10^{10}$vg/0.05mL</td>
<td>Change from baseline in BCVA and computerised visual field</td>
<td>No results available</td>
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<tr>
<td></td>
<td></td>
<td>NCT02645659*</td>
<td>19</td>
<td>48 weeks</td>
<td>II</td>
<td>1</td>
<td>(1) Administration of ascending doses of GS010</td>
<td>Incidence and severity of ADRs</td>
<td>No results available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT03428178*</td>
<td>120</td>
<td>12 months</td>
<td>N/A</td>
<td>1</td>
<td>(1) Single intravitreal injection of rAAV2-ND4 at a dose of $1 \times 10^{10}$vg/0.05mL</td>
<td>Change from baseline in BCVA</td>
<td>No results available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT02652767*</td>
<td>36</td>
<td>96 weeks</td>
<td>III</td>
<td>2</td>
<td>(1) Single intravitreal injection of GS010 in one randomly selected eye, at a dose of 9E10 viral genomes in 90μL balanced salt solution plus 0.001% Pluronic F68® (2) Sham injection to the eye not receiving GS010</td>
<td>Change from baseline in VA measured with an ETDRS chart in the eye treated with GS010 and in the eye injected with placebo</td>
<td>Improvement in BCVA from week 48 (+12.8 ETDRS letters in GS010 treated eyes and +11.8 ETDRS letters in sham-treated eyes) to week 72 (+20.6 ETDRS letters in GS010 treated eyes and +21.7 ETDRS letters in sham-treated eyes) Final results have not been published</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT02652780*</td>
<td>37</td>
<td>96 weeks</td>
<td>III</td>
<td>2</td>
<td>(1) Single intravitreal injection of GS010 in one of their randomly selected eyes, at a dose of 9E10 viral genomes in 90μL balanced salt solution (BSS) plus 0.001% Pluronic F68® (2) Sham injection to the eye not receiving GS010</td>
<td>Change from baseline in VA measured with an ETDRS chart in the eye treated with GS010 and in the eye injected with placebo</td>
<td>Improvement in BCVA from week 48 (+24.1 ETDRS letters in GS010 treated eyes and +20.3 ETDRS letters in sham-treated eyes) to week 96 (+28.1 ETDRS letters in GS010 treated eyes and +23.2 ETDRS letters in sham-treated eyes) Final results have not been published</td>
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<tr>
<td></td>
<td>scAVV2-P1ND4-v2</td>
<td>NCT02161380*</td>
<td>30</td>
<td>1 year</td>
<td>I</td>
<td>3</td>
<td>(1) Six patients with chronic bilateral visual loss &gt;12 months receiving either a single low dose ($5 \times e^9$vg) or a single medium dose ($2.46 \times e^{10}$vg) of scAAV2(Y444,500,730F)-P1ND4-v2 (2) Six participants with acute bilateral visual loss &lt;12 months receiving either a single low dose ($5 \times e^9$vg) or a single medium dose ($2.46 \times e^{10}$vg) of scAAV2(Y444,500,730F)-P1ND4-v2 (3) Two participants with unilateral visual loss receiving a single low dose ($5 \times e^9$vg)</td>
<td>Incidence and severity of ADRs</td>
<td>Groups (1) and (2): Average VA at month 12 improved of 0.24 logMAR for treated eyes and 0.09 logMAR in the fellow eye. Post-hoc analysis showed an improvement of VA at month 12 ($p&lt;0.053$) and month 18 ($p&lt;0.001$) when evaluating the difference between study eye minus fellow eye improvement. Group (3): one patient lost vision 3 months after treatment, the other patients lost three letters 6 months after treatment Final results have not been published</td>
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Table 1. (Continued)

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| Retinal tissues regeneration | Stem cells | NCT03011541* | 500 | 12 months | N/A | 3 | (1) Bone marrow-derived stem cells administered via retrobulbar, subtenon and intravenous for one or both eyes  
(2) Bone marrow-derived stem cells administered via retrobulbar, subtenon, intravitreal and intravenous for one or both eyes  
(3) Bone marrow-derived stem cells administered via either intraoptic nerve or subretinal for eye with worse vision with fellow eye receiving either retrobulbar and subtenon or retrobulbar, subtenon and intravitreal, followed by intravenous interventions | BCVA measured with a Snellen chart and ETDRS chart | BCVA improved in all five LHON patients enrolled from 1-month post treatment to 16-month post treatment. Improvement was evaluated as NLP, HM and CF |

AdRs: adverse drug reactions; BCVA: best corrected visual acuity; BID: bis in die (two times per day); CF: counting fingers; CRR: clinically relevant recovery; ETDRS: early treatment diabetic retinopathy study; HM: hand motion; LHON: Leber hereditary optic neuropathy; NLP: no light perception; NPMDS: Newcastle paediatric mitochondrial disease scale; OLE: open label extension; TID: tris in die (three times per day).

*R: Clirial trial ID according to the clinical trials database clinicaltrials.gov
**EudraCT number according to the clinical trials database clinicaltrialsregister.eu
Carelli et al. provided further evidence on the efficacy of Raxone in LHON patients, showing that an early start of treatment is linked to an increased visual recovery.\textsuperscript{7} Observations showed that (i) spontaneous recovery of VA is associated with a young age of symptoms onset, (ii) longer treatments were associated with vision recovery, (iii) m.11778 G\textgreater{}A carrier were the best responders, and (iv) involvement of the second eye was delayed in treated patients.

Further study on Raxone includes a phase IV clinical trial (post-authorisation; NCT02774005), which will evaluate the proportion of eyes with clinically relevant recovery in a 12-month period on a population of 250 patients affected from LHON caused by point mutations m.11778G\textgreater{}A, m.3460G\textgreater{}A and m. 14484T\textgreater{}C. Results are not available yet (Table 1).

Other researchers have tried to enhance antioxidant medicinal products as a possible treatment for LHON. Cysteamine bitartrate has been evaluated as possible treatment for LHON due to the role that might play in reducing oxidative stress. Cysteamine bitartrate is a diamine composed of a disulphide bridge, and is related to cystine, an important precursor of glutathione (GSH). Alterations in GSSG/2GSH ratio cause an increase of intracellular oxidation due to imbalance of intracellular metabolic function.\textsuperscript{12}

Treatment with cysteamine bitartrate was evaluated in a clinical trial (NCT02023866) carried out on a total of 36 paediatric patients between 2 and 17 years old affected by inherited mitochondrial diseases including LHON (Table 1). Patients were administered cysteamine bitartrate delayed-release capsules up to 1.3 g/m\textsuperscript{2}/day in two divided doses, every 12 h, for up to 6 months. The primary endpoint evaluated was change from baseline in Newcastle paediatric mitochondrial disease scale (NPMDS) sections I to IV did not reach statistical significance (section I: \(p = 0.1875\); section II: \(p = 1.0000\); section III: \(p = 0.0781\); section IV: \(p = 0.2941\)). A high percentage of serious adverse drug reactions (30.56\%) and non-serious adverse reactions (97.22\%) occurred in the treated population. A long-term extension clinical trial was started in 2015 (NCT02473445) but was terminated due to lack of cysteamine bitartrate efficacy demonstrated in the previous study (NCT02023866; Table 1). For this reason, cysteamine bitartrate was not included in the prospective treatment protocol (Figure 1).

Another investigational medicinal product is KH176, a small molecule (a Vitamin-E-derived molecule) currently under development to treat mitochondrial-related diseases. KH176 acts as a modulating agent, targeting ROS at intracellular level.\textsuperscript{13} KH176 has been studied in a phase I study (Figure 1) on healthy volunteers (NCT02544217) and the results indicate KH176 as safe up to a single dose of 800 mg and multiple doses of 400 mg twice daily but at doses of 800 mg and 2000 mg QT prolongations was observed\textsuperscript{13} (Table 1).

### Inhibition of apoptosis of retinal ganglion cells

In patients affected from LHON, blindness is caused by the apoptosis of RGCs. Apoptosis can be triggered by the peroxidation of cardiolipin,\textsuperscript{14} a unique anionic phospholipid which plays a key role in maintaining the curvature of mitochondria cristae. Deficiency of cardiolipin can lead to a reduced number of cristae, thus a decreased mitochondrial respiration and increased ROS production.\textsuperscript{9,15} Under these conditions of increased ROS production, cardiolipin migrates to the outer leaflet of the inner mitochondrial membrane where undergoes peroxidation due to the activity of a cardiolipin-specific peroxidase of cardiolipin-bound cytochrome C which promotes the release of pro-apoptotic factors.\textsuperscript{14,15}

Elamipretide is a mitochondria-targeting peptide, which reduces mitochondrial ROS and cytochrome C release, improving mitochondrial response to metabolic changes.\textsuperscript{16} Due to its high affinity to cardiolipin, its ability to reduce oxidative stress and to prevent cytochrome peroxidase activity, elamipretide protects the architecture of mitochondria cristae.\textsuperscript{9} By protecting mitochondria, elamipretide promotes an increased ATP production and decreased ROS production.

In 2016 ReSIGHT (NCT02693119), a phase II, randomised, double-masked, vehicle-controlled clinical trial (Figure 1) was started on 12 patients suffering from LHON caused by mutation 11778G\textgreater{}A. The primary endpoint evaluated was the incidence and severity of adverse events occurring at 56 weeks of treatment (Table 1). Final results have not been collected yet.

### Gene therapy medicinal products

About 70\% of LHON patients carry the mtDNA point mutation m.11778G\textgreater{}A which is associated with a low rate of spontaneous recovery (~4\% of cases). Targetting this mutation represents the ideal target to develop medicinal products to treat LHON.

GS010 (rAAV\textsubscript{2-}ND\textsubscript{4}) is a gene therapy medicinal product used to specifically treat the m.11778G\textgreater{}A affecting the ND\textsubscript{4} gene which is expressed only by the mitochondrial genome. GS010 delivers the missing gene using the ‘alloptic expression’, in which a nuclear version of the mitochondrial gene is recoded for expression and import into mitochondria using the AAV vector.\textsuperscript{8}

Six clinical trials on LHON patients harbouring m.11778 G\textgreater{}A have been performed between 2014 and 2019 to assess safety, efficacy and tolerability of GS010 in LHON patients. Before 2014, a clinical trial was carried out on nine LHON patients harbouring m.11778G\textgreater{}A mutation (NCT01267422) to evaluate changes in BCVA up to 3 years post treatment (Table 1). Out of nine patients undergoing a single-dose intravitreal injection of rAAV2-ND4, six
patients showed an improvement of 0.3 and 0.9 logMAR, two patients did not show a meaningful improvement in BCVA (improvement was <0.3 logMAR) and one patient did not show any improvement. None of the three patients who did not show improvements underwent electroretinogram examinations (one out of the three patients was too young and two out of three patients refused to have the examination), therefore the status of their retina is not known. The clinical trial has not been included in Table 1 because it was carried out before 2014. Clinical trials NCT01267422 has been described because of the importance it had in showing initial safety and efficacy of rAAV2-ND4.

Preliminary results of a clinical trial (clinicaltrials.gov: NCT02064569; EudraCT database 2013-001405-90) carried to evaluate safety of GS010 up to 48 weeks, showed humoral response against the viral vector (Table 1). In 2014, two randomised, parallel-assigned phase III studies, RESCUE and REVERSE (clinicaltrials.gov: NCT02652767 and NCT02652780, respectively; EudraCT database: 2015-001265-11 and 2015-001266-26, respectively) were started to evaluate the efficacy of GS010 in improving VA measured with an ETDRS chart (Table 1). In the RESCUE study, a total of 36 patients between 15 and >64 years old affected from LHON caused by m.11778G>A and having onset of visual loss for ≤180 days were enrolled and were randomly given an intravitreal injection into one eye of a solution containing GS010 and the other eye with a sham injection. Preliminary results at week 48 and week 72 were published from the sponsor.17 GS010-treated eyes showed an improvement from nadir at week 48 and week 72 (+12.8 letters and +20.6 letters, respectively) and from sham-injected eyes (+11.8 letters and +21.7 letters, respectively).17 According to clinicaltrials.gov, database of clinical trials, final results have been collected at week 96 (September 2019). In the REVERSE study, a total of 37 patients between 15 and ≥64 years old affected from LHON caused by m.11778G>A and onset of visual loss for ≥180 days and ≤365 days were enrolled and randomly given an intravitreal injection into one eye of a solution containing GS010 and the other eye with a sham injection. The sponsor of the study published preliminary results on REVERSE,18 showing continuous improvements in the logMAR score of patients treated eyes over 96 weeks. GS010-treated eyes showed an improvement from nadir at week 48, week 72 and week 96 (+24.1 letters, +27.4 letters and +28.1 letters, respectively) as well as sham-injected eyes (+20.3 letters, +22.6 letters and +23.2 letters, respectively). Final results will be collected in 2020 and data analysis will be performed.

BCVA has been further evaluated in a clinical trial (NCT03153293) carried out in 2017 in 142 LHON patients harbouring m.11778G>A after 12 months of GS010 treatment (Table 1). In the same year, GenSight Biologics carried out another clinical trial (NCT03293524), REFLECT a randomised, phase III trial in which patients with vision loss onset up to 1 year were treated with bilateral intravitreal injection of GS010 (Table 1). The REFLECT study evaluates BCVA in 90 LHON patients after 12 months of GS010 treatment. In 2018, a clinical trial was started (NCT03428178) and will evaluate BCVA in patients with onset of LHON symptoms from 3 to ≥60 months (Table 1).

Another approach with gene therapy is under evaluation using scAVV2-P1ND4, a different gene therapy medicinal product. One non-randomised, phase I trial (NCT02161380; Figure 1) has been started in 2014 to assess toxicity of scAVV2-P1ND4 injection on 30 patients suffering from LHON caused by mutation m.11778G>A. Initial results on five patients suggested scAVV2-P1ND4 to be safe. VA measured with ETDRS chart did not improve in three out of five patients, while one out of five patients had VA increase of seven letters (equivalent to three lines of vision) and one out of five patients had VA increased of 15 letters (equivalent to three lines of vision). Further results were collected on a population of 14 patients and suggested safety of scAVV2-P1ND4. Two out of 14 patients developed asymptomatic transient mild anterior uveitis which might be related to the injection of scAVV2-P1ND4.19 VA improved between baseline and post-injection and also between day 1 post-injection and month 24 post-injection (Table 1). Further data for this clinical trial will be collected.

Retinal tissues regeneration

RGCs are non-regenerative cells, therefore the loss of RGCs in LHON leads to optic nerve atrophy and patients to permanent blindness.5 No therapies are available to induce RGCs to regenerate, but researchers are evaluating possible treatments with bone marrow-derived stem cells (BMSCs), which are showing promising for neurologic and ophthalmic diseases.20

Stem Cell Ophthalmology Treatment Study (SCOTS) is an open label, non-randomised clinical trial (NCT03011541) evaluating the efficacy of BMSCs in patients suffering from ocular diseases, including LHON (Table 1). Five patients suffering from LHON caused by m.14484T>C (n=2), m.3460A>G (n=2) and m.4917A>G (n=1) were enrolled and BCVA using an ETDRS chart was evaluated after treatment with BMSCs. Different grade of improvement in VA and visual field had been observed in the five treated patients, occurring from 1-month post treatment to 16 months after treatment. Preliminary results are promising, but more studies are needed to proof efficacy of BMSCs in LHON.20

Conclusion

Treatment of LHON remains a great challenge in clinical practice. Clinical trials to evaluate medicinal products to
treat LHON are increasing in size and are being undertaken either in patients affected from mitochondrial diseases including LHON or specifically on LHON patients. According to the data obtained from the clinical trial databases clinicaltrial.gov and clinicaltrialsregister.eu, research has focused on Raxone, which is the only authorised treatment for LHON, and is now focusing on GS010, a gene therapy medicinal product which is showing promising results in treatment of LHON caused m.11778G>A. Results on efficacy in long term treatment with GS010 are awaited.

Authors’ note
The views expressed in this article are the personal views of the authors and may not be used or quoted as being made on behalf of, or reflecting the position of, any national competent authority, the EMA or one of its committees or working parties or any University.

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