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Developing safe and effective medicinal products to treat Leber Hereditary Optic Neuropathy. Clinical and regulatory challenges

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INTRODUCTION

Leber Hereditary Optic Neuropathy (LHON) is a rare maternally-inherited mitochondrial optic neuropathy caused by three mitochondrial DNA point mutations.

Raxone (idebenone) is the only approved medicinal product to treat LHON (MPLHON) within Europe. In the United States (US), Raxone was granted an orphan designation[1] and currently there are no FDA-authorised MPLHON.

AIMS

The aims of this study were:

1) To evaluate MPsLHON under development
2) To understand clinical and regulatory pathways pursued by pharmaceutical companies when developing MPsLHON

METHOD

Phase I: MPsLHON studied between 2007 and 2017 were identified from the EU clinical trials register and from the US national library of medicine database of clinical trials. Mechanism of action, site of action and the nature of the active substances were reviewed. A prospective treatment protocol for LHON was suggested.

Phase II: Clinical development programs (CDPs) of MPsLHON were reviewed and analysed using descriptive statistics. Emerging patterns in primary endpoints studied between 2007 and 2017 were identified and compared.

Phase III: A review of available regulatory pathways within the EU to obtain a license for orphan medicinal products was carried out.

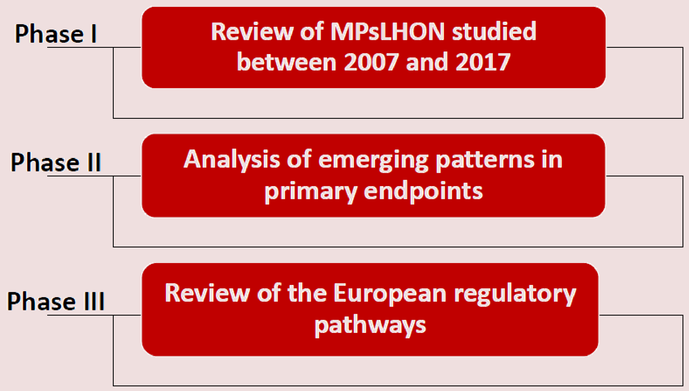

Figure 1 Overview of the methodology

RESULTS

Twenty-one clinical trials were included in the study and nine medicinal products were identified to be part of the suggested treatment protocol. According to the mechanism and site of action, MPsLHON were identified to treat the acute phase and/or the chronic phase of LHON. The analysis of the CDPs showed that the most common primary endpoints studied between 2007 and 2017 in 10 out of 21 clinical trials were visual acuity (VA) related (n=4 change in VA, n=2 best recovery in VA, n=2 best corrected VA, n=2 clinically relevant recovery in VA)

Raxone was marketed under exceptional circumstances and protocol assistance was requested during the development. An increased interest towards the viral vector rAAV$_2$-ND4 has been observed and to date rAAV2-ND$_4$ has an orphan designation in both the EU and the US.

Table 1 Identified Medicinal Products (N=9)

Category		Mechanism of action	Medicinal Product
Small Molecules (n=6)		Inhibition of Apoptosis	Cyclosporine A
			Elamipretride
			QPI-1007
		Modulation of mitochondrial electron transport chain	Idebenone
			KH-176
			Cysteamine bitartrate
Advanced Therapy (n=3)	*Gene Therapy*	"Fixing" gene therapy	rAAV$_2$
			scAAV$_2$
	Somatic Therapy	Reverse-disease therapy	Stem cells

Site of action: Mitochondria Retinal Ganglion cells

CONCLUSION

There is an increased interest in studying MPsLHON as shown by the increased number of clinical trials carried out and the number of drug classes explored. However, only two medicinal products are available on both the EU and US markets and LHON remains a disease with an unmet medical need.

REFERENCES

[1] US Food and Drug administration. Search Orphan Drug Designations and Approvals: Idebenone [Internet]. Silver Spring (US): Food and Drug Administration. Last Updated: 29/12/2017 [cited 12/09/18]. Available from URL: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/