



ODAK

Orphan Drug for Acanthamoeba Keratitis



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Final report for the ODAK project

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1 Executive Summary

ODAK is a research project to develop the Orphan Drug Polihexanide (PHMB) to provide a safe and effective drug for the treatment of Acanthamoeba keratitis (AK). This is a rare infectious disease caused by a free-living microorganism called Acanthamoeba, present in water, air and soil. The microorganism can cause a severe eye infection and is most often linked to contact lens wearing. Without treatment, this debilitating eye disease causes patients to suffer severe pain, vision loss and eye enucleation. Currently, there is no approved drug to treat this infectious rare disease although combinations of unlicensed anti-amoebic agents such as biguanides and diamidines have improved the treatment outcome of AK. However, these off label treatments use drug concentrations and treatment regimens based on empirical safety and efficacy data.

The primary deliverables of the ODAK project are:

- 1. Experimental scientific evidence on the quality, safety and efficacy of PHMB to provide the basis for a Marketing Authorisation in 2019;**
- 2. Recommendations to improve clinical practices in the treatment and management of AK based on the efficacy and safety evidence.**

The ODAK project advanced the preclinical and clinical research and development of the orphan drug PHMB (designation EU/3/07/498) as a safe effective treatment for AK. Innovative preclinical and clinical research activities were required to identify optimal PHMB formulations and develop the evidence base through Phase I (NCT02506257)–and Phase III (NCT03274895) clinical trials for a Marketing Authorisation Application for PHMB to provide a safe licenced drug to treat AK.

The ODAK project ended on 30th November 2017 with major progress made towards:

- The first safe and effective drug for treating AK - once launched this will deliver a new drug to the global rare disease markets creating a new revenue stream for SIFI and securing high skilled manufacturing jobs in Europe;
- A new gold standard of care for AK patients in Europe. This is the first optimised therapy regimen for any keratitis globally, adoption will improve the effectiveness and equality of care for European patients. This “standard of care” is expected to be adopted by clinicians across the globe.
- Awareness raising of the disease in Europe including public advice information, patient specific information and support materials, to help disease prevention.
- Raised awareness amongst a global clinical community about the disease and problems with misdiagnosis – this aims to reduce the current delays in AK diagnosis and improve clinical outcomes.
- A new cGMP production process for PHMB as both an active antimicrobial material for global markets to address unmet needs, and antimicrobial resistance, and as Nano-medicine drug carrier.

The project was delayed through a number of unforeseen events; 1) drug supply was halted early in the project due to a pharmaceutical takeover; 2) PK analysis was not possible to measure with current techniques at required limits of detection; 3) the closure of Moorfields Pharmaceuticals GMP facility and acquisition of this business unit by Rayner Pharmaceuticals Limited. Although these issues were overcome, the impact of these unforeseen events caused a significant delay in the start of the Phase



III clinical study. The project was successful in recruiting 17 AK patients into the Phase 3 trial in 4 months with no Serious Adverse Events recorded. A project extension was requested to complete the project but was refused by the EC project team. Partner 2 (SIFI) is in the process of raising funding to continue the trial, SIFI has guaranteed funding for treatment of the 24 patients currently in the trial. Recruitment is on-going.

The ODAK project will deliver better standards of care for patients providing an alternative to off label treatment and removes safety concerns limiting current dose regimens. This directly enhances patient quality of life and prevents blindness, eye loss and in extreme cases reduced lifespan of patients. The new ODAK drug will be affordable and reduce the burden on healthcare providers and societal of this disease. The ODAK PHMB product will create a new revenue stream for SIFI securing and creating high skilled science and manufacturing jobs within a European business. The drug is expected to be marketing by SIFI in the EU and reach a global market place through new strategic alliances with large pharmaceutical businesses.

ODAK directly contributes to the International Rare Diseases Research Consortium goals towards 200 new therapies, and the new IRDiRC Goals 2017-2027 to improve access to accurate diagnosis, care and therapy.

The Project partners were: Società Industria Farmaceutica Italiana (SIFI)- S.p.A. [Italy] – technical director and experts in ophthalmic drugs and med-tech; University of Rouen [France] – toxicology and project coordinator; Research Toxicology Centre S.p.A.[Italy] – toxicology and parasitology; Moorfields Eye Hospital [United Kingdom] – experts in treatment of AK and GMP manufacturing (in the early stages of ODAK); PSR Group B.V. [Netherlands] - designing and successfully implementing clinical trials targeting rare diseases; Ceratium Limited [United Kingdom] - European (FP7) project management and knowledge transfer. This consortium was supported by international experts in this eye disease and healthcare, and patient advocates.

2 Project context and the main objectives.

2.1 Project Context

Acanthamoeba Keratitis (AK) is a rare infectious eye disease affecting approximately 1 in every 1.000,000 citizens in the EU each year. Although incidence is low, the disease can be very severe and seriously debilitating. This is a potentially devastating eye infection for patients, causing vision deterioration, blindness and eye enucleation.. Many patients report very high levels of intense pain.

The infection is caused by *Acanthamoeba spp.* a common protozoan present in water, soil, and the air. This microbe has a cyst stage making it very hard to treat with conventional antimicrobial drugs and there are no approved drugs for this disease. In recent years combinations of unlicensed anti-amoebic agents such as biguanides and diamidines have greatly improved the treatment outcome of AK but drug concentrations and treatment regimens are based on empirical safety and efficacy data.

ODAK is an industry led project mobilising the critical mass of industry, pharmaceutical and academic expertise to develop the Orphan Drug polyhexamethylene biguanide also known as Polihexanide (PHMB). The project targets an unmet clinical need to optimise therapeutic approaches to alleviate the severe negative impacts of AK on the health and quality of life of patients. Preclinical and clinical research and innovation work has been required to identify optimal PHMB formulations and develop the evidence base through Phase I and III clinical trials for a Marketing Authorisation Application for



PHMB to provide a safe licenced drug to treat AK. Recommendations for the best dose-benefit treatment are needed by the clinical community, the Phase III clinical trial is addressing this to deliver an evidence based new “gold standard” treatment regimen.

ODAK directly contributes to the initial International Rare Diseases Research Consortium goals towards 200 new therapies, and the new IRDiRC Goals 2017-2027 for all patients to have access accurate diagnosis, care and therapy. The project has the potential to deliver better standard of care for patients providing an alternative to off label treatment and removes safety concerns limiting current dose regimens. This directly enhances patient quality of life and prevents blindness, eye loss and in extreme cases reduced lifespan of patients. The ODAK project is contributed to facilitating another product (PHMB) to apply for Market Application.

The ODAK project consortium of six European partners is led by SIFI a leading Italian pharmaceutical company dedicated to research, development and manufacturing of innovative safe drugs for eye care. SIFI have coordinated the development of the consortium to ensure the necessary skills to implement the ODAK work plan. The six partners include experts in ophthalmic drugs and med-tech (SIFI), toxicology (RTC), parasitology (UOR), designing and successfully implementing clinical trials targeting rare diseases (PSR, MEH) and European (FP7) project management and knowledge transfer (CERAT).

2.2 ODAK Aims and Objectives

The ODAK project aimed to undertake preclinical and clinical research on the Orphan Drug PHMB. The main objective was to provide a safe and effective drug for the treatment of the rare ocular disease Acanthamoeba keratitis (AK) tested according to international regulatory standards. Protocol Assistance was obtained from the European Medicines Agency on the drug development research plan. The protocol incorporated EMA advice to include a non-clinical phase, a double-blind placebo-controlled Phase I trial and a randomised double-blind, active controlled, parallel group Phase III study (efficacy and safety therapeutic confirmatory study).

The primary deliverables of the project are:

- 1) experimental scientific evidence on the quality, safety and efficacy of PHMB to provide the basis for a Marketing Authorisation within 5 years;
- 2) recommendations aiming to improve clinical practices in the management of AK based on the efficacy and safety evidence.

Work packages for gathering preclinical and clinical data together with management and dissemination activities were developed as follows:

WP1: Pharmaceutical Technology: Manufacturing and release of laboratory scale PHMB batches at different concentrations (0.02%; 0.04%; 0.06%; 0.08%) for investigative non-clinical studies and pharmaceutical development of PHMB eye-drops. WP1 objectives include:

- The development of a PHMB formulation that meets with stability, efficacy and safety criteria for ophthalmic administration;
- Analytical methods development and validation, for raw material, in process control, product release and stability study of PHMB formulations;



- Manufacturing and release of laboratory scale batches for investigative non-clinical studies: in vitro pharmacodynamics; in vitro cytotoxicity, PK animal study, investigative tolerability and in vivo efficacy studies.

WP2: Non-Clinical Studies: designed to meet regulatory compliance and to support the choice of a candidate formulation for Phase III clinical development.

- To undertake non-clinical pharmacokinetics, toxicology and pharmacodynamics studies designed to prepare for regulatory compliance studies and to support the choice of candidate formulations (different concentrations of PHMB) for clinical development.

WP3: Manufacturing Product: undertaking the manufacturer of PHMB batches for the main non-clinical studies as well the Phase I and Phase III clinical studies. WP3 objectives:

- Complete the manufacture and finished product testing of ODAK stability batches under aseptic conditions;
- Completion of an ICH stability study on the ODAK stability batches to generate data to support the product shelf life;
- Complete the manufacture, finished product testing and QP release of ODAK clinical batches to be used in clinical studies.

WP4: Clinical Studies: To execute the clinical development plan for PHMB in the treatment of AK by completion of:

- a retrospective study of AK patients and treatment;
- a phase I study in healthy volunteers;
- a phase III pivotal study in AK patients.

WP5: Regulatory affairs: To ensure work packages 1, 2 and 3 meets regulatory requirements for marketing authorization

- Identify all relevant EU guidelines for drug for human use;
- Ensure practical work meets the regulatory quality requirements;
- Assemble regulatory documents for submission of (e-CTD, Module 1);
- Support in preparing of other regulatory documents [e-CTD, Modules 2, 3, 4 and 5];
- Prepare an Application for Marketing Authorisation. Management of relations with the EMA and open discussions with other international competent authorities.

WP6: Project management: To ensure the most efficient and effective co-ordination and management of the project to meet the most important objectives within the expected period.

WP7: Communication, Dissemination and Exploitation: To ensure effective engagement with key stakeholders and patients, and ensure the optimal use and impact of the project results through a series of targeted and generic dissemination and exploitation activities throughout the project. To produce outreach and knowledge transfer resources to effectively communicate ODAK results to a wider and non-expert audience. The ultimate objective is to improve the health care provision for AK patients by identifying the safest and most effective PHMB product for treating patients with Acanthamoeba keratitis (AK) and optimising the treatment regimen for patients.

- Guidelines for an optimised therapy regimen and PHMB based treatment efficacy;
- Recommendations of best practice for AK patient care;
- Raising awareness of AK risk factors and preventative measures;



The main target groups will include: vision scientists and clinicians; patients; policy makers including the EC and national or regional health care decision makers; EMA; contact lens wearers (CLW) as an “at risk group”; the eye care industry and their suppliers; the general public; science and industry communities; media; third sector organisations involved in eye disease, patients, prevention and treatment.

3 S & T results/foregrounds.

3.1.1 Results of non-clinical studies

3.1.1.1 Drug formulation

Pre-formulation studies screened ophthalmic preparations of PHMB for suitability, and a formulation stability-indicating method was developed and validated for the raw material (PHMB 20% solution) with respect to specificity, linearity, accuracy, precision, detection limit: based on S/N ratio, quantitation limit: based on S/N ratio and System suitability. Stress stability screening was conducted on candidate formulations, and a formulation for further studies was selected.

With the aim of developing a final multi-dose PHMB formulation for eye-drops without the need for a separate preservative, a preliminary preservative efficacy study of PHMB at different concentrations (0.02%; 0.04%; 0.06%; 0.08%) was performed according to the current European Pharmacopoeia. The results for the efficacy of the antimicrobial preservation test, reported in terms of the reduction in number of viable microorganisms from the initial inoculum, showed that all PHMB test concentrations satisfied the “B” criteria of preservatives for ophthalmic preparations. Following this result and in agreement with the EMA advice of July 2014 it was established that production of the final PHMB eye-drops batches would be in unit dose plastic bottles (preservative-free) obtained by Blow Fill and Seal technology.

3.1.1.2 Stability studies

A stability study plan was set up, for each unit-dose clinical batch according to ICH Q1A: Stability testing of new drug substances and products. The plans include long term, intermediate and accelerated conditions. At every assigned time point, each batch underwent a complete set of analysis, to test the quality of the product. The study results allow us to set the shelf life of the product and the relevant storage conditions, according to ICH Q1A. In particular, a six-month accelerated stability study of the product has anticipated final storage condition. In addition, the ODAK project will continue the stability-testing period for an additional 24 months after the preparation of a formulation to determine the shelf-life of the final product.

3.1.1.3 Efficacy results

The efficacy of Polihexanide (PHMB) eye-drops against *Acanthamoeba* was investigated *in vitro* by an ATP-bioluminescence assay and in an *in vivo* rat model of keratitis. The purpose of the study was to assess the efficacy of PHMB at different concentrations against *Acanthamoeba polyphaga* using *in vitro* and *in vivo* test systems.

In vitro: Trophozoites of *Acanthamoeba polyphaga* ATCC 50495 were cultured in peptone yeast extract-glucose (PYG) medium at 25°C. Then 5×10^6 amoebae/ml were collected by centrifugation for 10 min at 150×g and induced to encyst by using Neff’s constant-pH medium at 31°C for at least 2 weeks. A linear correlation curve among amoebae number (haemocytometric count) and Relative



Light Unit (RLU) was produced. The ATP-bioluminescence assay (Pallcheck® System) was validated with respect to the traditional count method. Efficacy of 1/10, 1/100 and 1/1000 dilutions of PHMB (0.02%, 0.04%, 0.06% and 0.08%) was tested by using the ATP-bioluminescence assay. Killing kinetic curves were created using $> 5 \times 10^4$ cysts suspension exposed for 30 min, 1, 3 and 7 hours to 1/10 and 1/100 dilutions of the above selected PHMB concentrations. Statistical analysis was conducted by two-way ANOVA plus Bonferroni post-test. The ATP-bioluminescence assay showed that only 1/10 and 1/100 dilutions of the selected PHMB concentrations (0.08%, 0.06%, 0.04%, 0.02%) reduced cysts viability by 80% and 50% respectively. To determine the most effective PHMB solution a killing curve was generated with 100-fold dilution of the selected PHMB concentrations. The curve showed that reduction of cysts viability at 3h was 60% with PHMB 0.04%, 0.06% and 0.08% 100-fold diluted compared to PHMB 0.02% 100-fold diluted with a 40% reduction on cysts viability.

In vivo: Five weeks old Sprague-Dawley male rats were injected in the left cornea stromal layer with 104 trophozoites (*Acanthamoeba polyphaga*, ATCC 50495). A subconjunctival injection of 0.57 mg long-acting betamethasone was administered, and clinical examination was performed weekly. Rats inoculated with *Acanthamoeba polyphaga* were divided into 6 groups and topically treated 4 times a day with PHMB (0.02%, 0.04%, 0.06% and 0.08%) or a combination of PHMB and Propamidine (0.02% and 0.1%, respectively). Control animals were treated similarly with PHMB vehicle. Clinical infection was defined by corneal oedema and/or infiltration (associated or not with neovascularisation). Keratitis opacity lesions were scored from grade 0 (no lesions) to grade 3 (corneal opacification obscuring iris vessels details) according to Polat et al., 2014. At day 28, the rats were sacrificed. Corneal scrapings were performed for bacterial and parasitological cultures and real-time PCR analyses (Qvarnström et al., 2006). Paraffin-embedded corneas were analysed after hematoxylin-eosin and Schiff periodic acid staining. All animal procedures were performed according to the appropriate national and European guidelines and regulations for the Use of Animals, in Research. Statistical analysis was performed by estimating the significance using Fischer's exact tests. Our keratitis model showed that PHMB 0.04% and 0.06% significantly prevented corneal lesions worsening between day 14 and day 28 compared to the control group. We could observe the same tendency for PHMB 0.08%, although this was not significant. PHMB 0.02% also in combination with Propamidine is less effective than the other PHMB concentrations. PHMB 0.04%, 0.06% and 0.08% significantly decreased cultures/PCR and/or histology positivity compared to the control group.

Summary of key results: These *in vitro* and *in vivo* test systems have provided the same results identifying 0.02% PHMB as the least effective formulation against *Acanthamoeba polyphaga*. In addition, *in vivo* data confirmed that monotherapy with PHMB solutions at concentrations equal or more than 0.04 % seems to be effective against *Acanthamoeba polyphaga*. This experimental approach has provided a very useful preliminary tool for selecting the most appropriate PHMB concentration to be tested as drug candidate for clinical use.

3.1.1.4 Ocular tolerability assessment of PHMB 0.8%, 0.25% and 0.08% ophthalmic solutions

The objective of the study was to establish if PHMB 0.08% eye-drops was sufficiently safe to be tested in healthy human volunteers. In accordance with the European Medicines Agency Guideline on repeated dose toxicity CPMP/SWP/1042/99, a low concentration (0.08%) of PHMB eye-drops with established therapeutic effect, and an intermediate concentration (0.25%) of PHMB eye-drops, together with a high concentration (0.8%) of PHMB, eye-drops were selected. These formulations



were used in a two-week tolerance/toxicity study in rabbit to enable identification of toxicity. Treatments included: 50µL of PHMB vehicle (Group 1), PHMB 0.08%, 0.25% and 0.8% eye-drops (Groups 2, 3 and 4). The treatment was administered, 13 times a day at approximately 1-hour intervals from Day 1 to 7 (first week) and 7 times a day at approximately 2 hours intervals from Day 8 to 14 (second week). The left eye remained untreated. Two animals per sex of Groups 1 and 4, were sacrificed after 1 week of recovery. Ocular irritation assessment was performed daily, before first dosing, in all animals during the treatment and once daily during the recovery period. In addition, fluorescein staining of cornea, slit-lamp examination and ophthalmoscopy were performed at weekly intervals in all animals during the study. Macroscopic and microscopic examination of treated and untreated eyes were performed in all animals at the end of the treatment.

Slight conjunctival redness with slight/moderate discharge was noted in few animals treated with PHMB 0.08% and 0.25% eye-drops (Groups 2-3). Recovery occurred in all animals after the treatment period. No treatment-related changes were observed in the eyes of animals of these two Groups after microscopic examination. Assessment of ocular irritation, including fluorescein staining of the cornea, slit lamp examination and ophthalmoscopy, together with microscopic examination of the treated eyes and associated tissues, did not suggest any relevant treatment-related effect of PHMB ophthalmic solutions at 0.08% and 0.25%. PHMB 0.8% eye-drops (Group 4) induced moderate/severe treatment-related effect, increasing with the treatment period, causing irreversible damage to the eye. However, even in Group 4 (10-fold the anticipated dose in Phase I clinical trials), histopathological evaluations of the eye lens showed no degenerative changes. Moreover, for all tested PHMB eye-drops no indication of systemic effects were observed during the period of the study.

Summary of results. The data indicated that 2-week repeated instillation of PHMB 0.08% and 0.25% ophthalmic solutions in the rabbit eye did not show any relevant treatment-related effect. Only animals treated with PHMB 0.8% eye-drops showed moderate/severe treatment-related effects with irreversible ocular toxicity during the follow-up period. The observed microscopic changes in the Group 4 were from minimal to mild severity (i.e., grade 1 or 2 out of 4) and consisted of combination of conjunctival/corneal oedema, necrosis, iris congestion and acute inflammation. However, even in Group 4 (PHMB 0.8% eye-drops), histopathological evaluations of the eye lens showed no degenerative changes. Moreover, for all tested PHMB eye-drops no indication of systemic effects were observed during the period of the study. These findings, demonstrating the safety of PHMB 0.08%, supported our plan to select this concentration of PHMB eye-drops as an orphan drug for the treatment of *Acanthamoeba* keratitis in the Phase I clinical trials.

3.1.1.5 Pharmacokinetics Analysis (PK)

Multiple efforts and different attempts were made by RTC and then Intertek (a SIFI subcontractor) to develop a suitable analytical method for the determination of PHMB in biological matrices. This was not successful. Several experts were consulted, but none offered suitable methods, and the difficulties were supported by two academic studies published by Vonterbel et al. (J Clin Exp Ophthalmol 2015, 6:3) and by Horner et al. (J. Phys. Chem. B 2015, 119, 10531–10542). We also investigated radiolabelling of PHMB as a possible solution but following consultation with the EMA this was not required.

SIFI on behalf of the ODAK Consortium consulted the EMA about the problems with PK analysis. Based on our explanations and justification, experts at the EMA agreed with our proposal not to undertake PK analysis. Given that we found the determination of PHMB in plasma was not possible using current



technology, the EMA suggested an additional histological examination of different potential target tissues in the 26-week rabbit local tolerance/toxicity study to address the lack of an in-depth PK investigation. The histological examination was undertaken and completed by RTC with no significant negative findings.

3.1.1.6 A 26-week repeated-dose toxicity study of PHMB 0.08% ophthalmic solution

The objective of the study was to evaluate PHMB 0.08% eye-drops following repeated ocular administration in rabbit over a period of 26 weeks. One group of 8 male and 8 female NZW rabbits (Group 2) was treated by ocular application into the right eye of one drop of the test item (PHMB 0.08% eye-drops). Animals were treated 16 times/day at approximately 1-hour intervals from Day 1 to Day 5, 8 times/day at approximately 2-hour intervals from Day 6 to Week 3 (Day 21) and 4 times/day at approximately 4-hour intervals from Week 4 to Week 26. The left eye remained untreated. A similarly constituted control group was treated in the same manner with the control drop (Group 1). All animals were examined with slit lamp and indirect ophthalmoscope prior to allocation, on Day 1 before the first dosing and thereafter at weekly intervals prior to the first daily dosing. Animals with no ocular abnormalities were selected for the study. In addition, corneal fluorescein staining, slit-lamp examination and ophthalmoscopy were performed at weekly intervals in all animals during the study (Baldwin et. al., 1973). All animals of Groups 1 and 2 were sacrificed after 26 weeks of treatment and tissues/organs were collected to assess local and systemic toxicity. Macroscopic and microscopic examination of treated and untreated eyes were performed in all animals sacrificed at the end of the treatment.

After 26 weeks of administration no deaths and no significant clinical signs were observed during the study. No treatment-related lesions were detected at the weekly examination in the treated animals. The body weight of animals was not affected by treatment and no relevant changes in food consumption were observed in males and females during the study. Regarding clinical pathology, the haematology and clinical chemistry (at 13 and 26 weeks) did not indicate significant treatment related effects. Similarly, no treatment-related changes were reported at the histopathological examination of the eyes, or in the remaining examined organs/tissues. The lesions reported in control and/or treated animals, such as congestion and/or oedema in lungs and some other organs/tissues, physiological involution of thymus or pigmentation (hemosiderin like) in the spleen, had comparable incidence in the control and treated groups and/or are known to occur spontaneously in untreated New Zealand White rabbits of the same age, under the experimental conditions.

Summary of results: The results indicated that 26-week repeated instillation of PHMB 0.08% ophthalmic solutions in the rabbit eye did not show any relevant treatment-related effect. These findings support the development of PHMB 0.08% eye-drops as a safe and effective orphan drug for long-term treatment of *Acanthamoeba* keratitis.

3.1.2 Drug production

3.1.2.1 PHMB eye-drops batches production

During the project the GMP manufacturing facility (Moorfields Pharmaceuticals) at MEH closed. SIFI have an in-house manufacturing facility and were able to take over this work during the project to produce the PHMB eye-drops batches, under aseptic conditions, SIFI also undertook testing of PHMB stability.

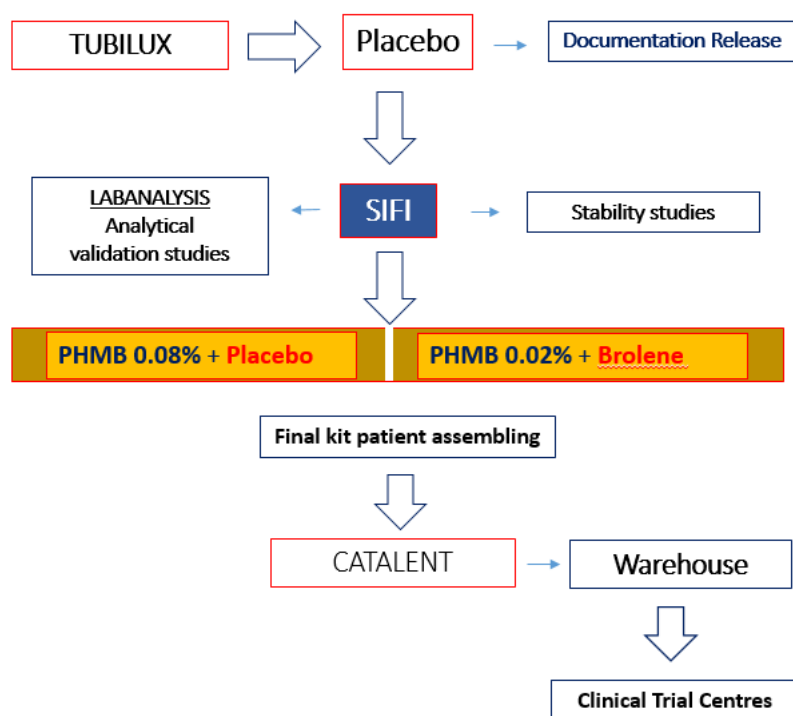


SIFI utilized the blow-fill-seal (BFS) technology, which is a form of advanced aseptic manufacturing. In the BFS the container is formed, filled, and sealed in one continuous, automated system. In the container blowing step, plastic beads are melted at high temperature and formed into a hollow tube, which is cut to the desired length. Two halves of the container mold close around the tube, and air is blown into the tube to expand it into the shape of the container. The partially-cooled container is immediately filled and sealed.

The manufacture of the finished products, testing and QP release of PHMB clinical batches to be used in the PHMB clinical studies was undertaken according to the scheme below.

All the manufacturing steps related to PHMB eye-drops 0.02% and 0.08% were made at SIFI by BFS in full compliance with the EEC cGMP. SIFI performed operations of manufacturing, primary and secondary packaging of the PHMB eye-drops, secondary packaging of the placebo and assembling of the patient kits (except for the addition of Brolene bottles which were purchased and added in the kit for the patient by Catalent (UK). At this site Brolene bottles were relabeled and the final kit assembled and released to the final clinical destination sites (UK, IT, PL).

For the patient kits assembly, due to the complexity of Phase III clinical, it has been also involved Tubilux Pharma S.p.A. (Italy) for the manufacture of the placebo and its primary packaging.



Completion of an ICH stability study of the PHMB eye-drops batches (analytical validation), in order to validate analytical methods used by SIFI to support the product shelf-life, has requested the external support from LabAnalysis (IT). A company working routinely with SIFI. This lab was able to validate Gel Permeation Method to determine potential impurities in the eye-drops as well UV method to be used by SIFI for the determination of PHMB concentration in routine stability-indicating method.



3.1.2.2 Future PHMB eye-drops development plan

The first clinical supply batches have been utilized to start Phase III trial in three countries (UK, PL, IT) where 24 patients with Acanthamoeba keratitis have been treated until today.

Following the EC decision to deny an extension of the project beyond the deadline of 30 November 2017, the continuation of the manufacturing process has been destabilised. However, the ethical issue is so huge that SIFI will make all the necessary efforts to proceed effectively with this activity. Only in this way it will be possible to guarantee recruitment, inclusion and treatment of all the expected 130 patients as agreed with the European Medicine Agency.

The next step will be to prepare another batch of clinical supplies (due to the expiry date of Brolene eye-drops as comparator). It is expected the release of new clinical supplies batch in May-June 2018.

Simultaneously, SIFI SpA will proceed with the PHMB synthesis under GMP conditions following development at a Contract Manufacturer). After the first batch production, a biosimilarity study with the previous PHMB produced by Lonza will be carried out and results collected in the Module 3 of the Common Technical Document.

After conclusion of the recruitment of the Phase III trial, SIFI commits itself to proceeding with the Marketing Authorization Application. Accordingly, Module 3 (quality data) and Module 4 (non-clinical data) will be updated and as soon clinical documentation will be ready all these together with Module 5 (Phase I and Phase III clinical data) will be submitted as documentation requested by EMA for the application of Marketing Authorization of our product.

3.1.3 Clinical Studies results

3.1.3.1 Results of a 10-year retrospective study in Italy and in the United Kingdom

The purpose of the 10-year retrospective study was to evaluate the clinical outcome of patients affected by AK treated with unlicensed drugs. In this 10-year retrospective study, records from patients affected by AK treated from 1997 to 2007 at Moorfields Eye (UK) and San Raffaele (Italy) hospitals were selected. The study protocol was approved by the Ethics Committees. The primary end-point of the study was the clinical resolution rate (CRR) defined as percentage of patients cured 1 month after discontinuing all therapies. Secondary end points of the study were visual acuity, rate of patients requiring keratoplasty, duration of treatment, incidence of adverse events (AEs). A descriptive statistic was performed. One hundred patients were evaluated, ninety-six were contact lens wearers. In 84 cases diagnosis was based on either culture or histology. The mean time delay between the onset of symptoms and diagnosis was 51 days. Infiltrates (24%) and pain (50%) were the most common signs and symptoms observed, respectively. Many patients (40%) had very low vision at diagnosis.

Efficacy: Overall, most patients (83%) were treated with multiple agents. PHMB was the most commonly used drug whereas PHMB and a diamidine (hexamidine or propamidine) were widely used as combination therapy (51% of cases). The median duration of treatment was 139 days.

The overall CRR was 86%. Keratoplasty was performed in 24 patients: 14 patients not cured medically had therapeutic or tectonic keratoplasty whereas in 10 patients keratoplasty was executed to restore vision.



The outcome of AK was considered based on the different treatments allocated to patients. Patients treated with monotherapy (PHMB or Chlorhexidine) had a higher CRR (96-100%) than those treated with combination therapy (80-90%). At the end of the study an improvement in visual acuity (range 0.1 to 0.8 decimal) was described for 56 patients whereas 25 patients had very low vision.

Safety: A total of 31 Adverse Events (AE) occurred during the study, 21 had a relationship to treatment; 19 AEs were considered serious. The most common AE reported was ocular toxicity (n=10) which occurred in 9 patients. 6 cases were related to the use of diamidines and 3 cases to that of biguanides (2 to PHMB).

Summary of results: PHMB was the most used medication for patients with AK in this study. These data suggest that PHMB used as monotherapy for treating AK has a good risk to benefit ratio and is a good candidate for a new drug licensing application.

3.1.3.2 ODAK Phase I Clinical study: Ocular safety and tolerability of high dose PHMB in healthy volunteers (NCT02506257)

To evaluate the safety and tolerability of three dose levels (0.04%, 0.06% and 0.08%) of preservative-free PHMB, a Phase I study was performed in healthy volunteers. These doses were previously evaluated and found safe in rabbits in a 26-weeks ocular toxicity/tolerability study. This was a double-masked, placebo-controlled, parallel-group multicentre Phase I study (Study code 042/SI). Ninety volunteers (44 M/46 F, age 18-55 years) were randomised to 1 of the 4 study arms: 0.04%, 0.06%, 0.08% PHMB and placebo, in a 3:3:3:1 ratio, respectively. All formulations were preservative-free. Subjects were dosed with an intensive regimen mimicking that one used during the first month of treatment in patients with *Acanthamoeba keratitis*. The study was approved by local ethics committees (trial registration number: NCT02506257). Systemic and ophthalmological safety data were recorded. The primary outcome measure was the rate of dose limiting events (DLEs) leading to interruption of dosing. The frequency of treatment emergent adverse events (TEAEs) as well as serious AEs (SAEs) starting after the first administration of the study drug were also computed. The rate of occurrence of SAEs, DLEs and TEAEs were compared between groups by Fisher's exact test. Statistical tests were performed 2-sided and with a 5% significance level. A 95% confidence interval for the difference between each respective dose and placebo and p-value was calculated.

Summary of results: there were no clinically significant changes in vital signs and laboratory values. Only 5 subjects had events leading to premature withdrawal of treatment (DLEs). No statistically significant differences (Fisher's exact test) were observed between any of the treatment groups. The onset of events occurred shortly (day 0 to 4) after first exposure to treatment and all were resolved between 1 to 15 days. No statistically significant differences in the occurrence of events related to treatments (TEAEs) were observed between groups with the exception of 0.06% PHMB vs. 0.04% PHMB groups ($p=0.005$, Fisher test, $\alpha=0.05$). The most common adverse events, reported by $\geq 10.0\%$ of subjects were conjunctival and corneal staining, eye pain and conjunctival hyperemia.

Conclusions: An intensive regimen with concentrated PHMB eye-drops was safe and well tolerated in healthy volunteers. According to this data, 0.08% PHMB will be tested in a Phase III study in patients with *Acanthamoeba keratitis*.

3.1.3.3 ODAK Phase III clinical study (NCT03274895)

The objective of the Phase III clinical study is to evaluate the efficacy, safety and tolerability of monotherapy 0.08% PHMB ophthalmic solution compared to vehicle/placebo and the conventional,



combination therapy of 0.02% PHMB and 0.1% Propamidine (Brolene) in subjects affected by Acanthamoeba Keratitis (AK). The trial design is a randomized, double-masked, double-dummy, active-controlled, multiple centre, parallel-group study. The trial requires 130 AK patients aged 14 or over, assigned in a ratio of 1:1 to the two therapies. The placebo is required to keep the study masked and is produced in a multi-dose eye-drops bottle almost identical to Brolene®.

An evaluation of the local clinical trial expertise, necessary infrastructure and access to the target patient population was undertaken by PSR. This site and cost evaluation was done under a transparent and equal process. A decision on the best site to be contracted for the study was based on a best price/quality ratio taking into account the clinical issues critical to patient safety and trial delivery.

The decision on suitable sites for selection was made through a formal structured process. This is industry standard and performed within the ICH-GCP guidelines and the EU Clinical Trial Directive. The process includes the following aspects:

1. Potential sites are short listed: Project teams including clinical experts, the CRO and advisors, including Key Opinion Leaders (clinicians who are experts in the disease area) identified potential study sites;
2. Expressions of interest and feasibility assessment: A request was made directly to the clinical team or clinical trial unit at selected potential study centres for an expression of interest. This may not go through a normal procurement and tendering process. Instead, a feasibility questionnaire was sent about the trial. This was used to assess likely patient numbers; local capacity to undertake the trial; facilities, level of interest; previous experience of studies; etc.
3. Site Qualification Visit: Potential sites meeting study criteria based on the feasibility questionnaire were short listed and a site qualification visit undertaken to make an in-depth assessment of the site suitability. A final selection of primary study sites and reserve sites has been made based on the most appropriate sites for the study.
4. Pricing: The cost of the study at different sites forms part of the selection criteria for our studies, we adopt a best value for money approach. For rare disease studies, in practice price is rarely a key issue. CROs report pricing is relatively consistent and many CROs adopt pricing models based on past experience allowing per patient costs to be estimated quite accurately. In some MS (e.g. UK) a fixed pricing model is being adopted. In our experience adopting a lowest price approach would not be sensible, to date pricing is rarely a key issue but the capacity and ability of a subcontracted site to undertake the study is critical.

Following this procedure, 23 sites were short listed for the Phase III trial. After internal meetings with experts, 21 sites in Germany, Italy, Poland, Portugal, UK, Ireland and Spain, were contacted between June and September 2016 to complete a study specific questionnaire. 17 sites completed the questionnaire in this period; 4 sites were not interested or declined to complete the questionnaire. From these, 9 sites were rejected as patient numbers were too low or they did not have the required equipment needed for the study. Site selection/qualification visits for the remaining 8 sites took place between August and September 2016. 6 sites were selected and contracting with these sites was performed in the first quarter of 2017. For the 6 selected sites (3 in UK, 2 in Italy, 1 in Poland) all necessary submissions to the Competent Authorities and Central Ethics Committees were performed in Q1 (UK/Italy) and Q2 (Poland) 2017.



In the UK the CA approval was obtained within 2 months. Although the package was validated within one week, there were delays in obtaining EC and HRA approval due to questions related to the clinical trial agreement between Sponsor and participating hospital. Also, there was uncertainty related to the non-commercial/commercial status of an EC funded trial in UK.

In Italy the EC approvals at Venice and Milan were obtained after 2 months. There was a major delay in obtaining AIFA approval (7 months after initial submission). In addition to their questions about IMP dosing, safety and manufacturing/quality aspects of the IMP, there were frequent technical difficulties of the AIFA portal, long intervals in questions and answers, and the summer holiday period.

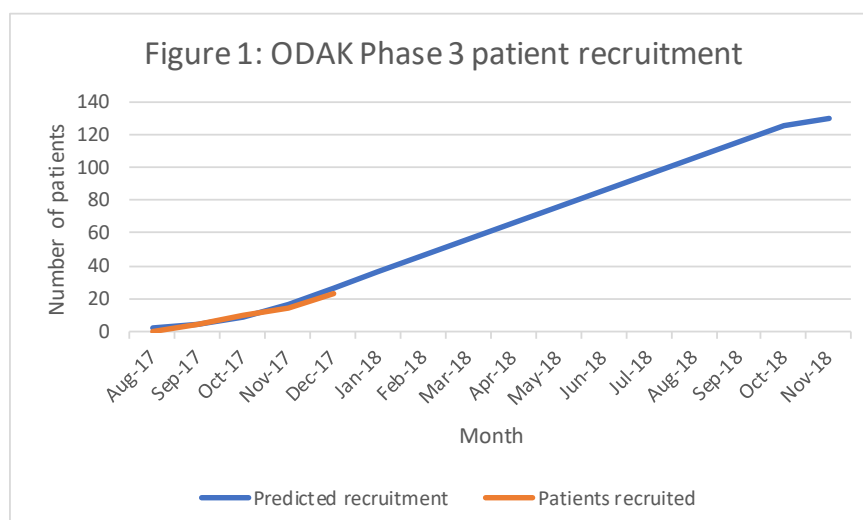
In Poland the EC approval was obtained within 2 months. CA approval took 6 months due to questions related to the IMP and patient information.

In addition to the above, PSR completed the following study preparations: Writing of all necessary study documents (informed consent form, worksheets, training materials, etc); Writing of all required study plans and manuals (safety management, monitoring, study operations manual etc); Set-up of the Trial Master File and Investigator Site Files; Set-up of the clinical database (electronic CRF); Performance of the Site Initiation Visit.

On March 17th/18th 2017, an investigator's meeting was conducted at Moorfields Eye Hospital in London. Representatives from all clinical sites, as well as representatives from SIFI, PSR and Ceratium attended this meeting to be trained on the study protocol, as well as the study procedures and logistics.

The First Patient was randomised at the Moorfields Eye Hospital at the 17th of August 2017. Moorfields increased the recruitment rate in the following months by recruiting 5 patients in September, 4 patients in October and 7 in November, to a total of 17 patients at the 30th of November 2017. Other UK sites could not be activated due to issues with internal (pharmacy) logistics, in Italy and Poland no AK patients visited the hospital after all regulatory approvals were obtained. To maintain quality, accuracy and integrity of clinical data, and adherence to protocol and ICH-GCP, monitor visits were performed by PSR at all sites with active patients.

In December, 3 other sites in UK and Italy started recruitment; 1 patient in Manchester, 1 patient in Milan and 2 in Venice. With 2 additional patients at Moorfields, the total amount of 23 patients was reached in December 2017. Recruitment was on target with predictions, see Figure 1.





The start of the trial was very delayed due to unforeseen issues, primarily the takeover of the drug manufacturer at an early stage in the project creating major delays in obtaining suitable PHMB raw material. A request for a project extension was made to the EC highlighting the nature of the delays, in the view of the ODAK team this met the EC criteria of significant unforeseen delays as reasons an extension would be made. The proposal evaluated by experts had clearly stated the EC FP7 grant was required to support the clinical trial. Despite support from leading European clinicians, patients, the rare disease community, and industry, the EC refused to grant an extension to the ODAK project to complete the clinical trial. To our knowledge the ODAK project is the first clinical trial project to have had an extension request denied. The reasons given were based on administrative and contractual issues. The EC decision is a direct threat to the on-going clinical trial by removing access to the critical unspent FP7 grant funding. It is unclear whether further drug development will continue at this stage. SIFI has guaranteed patients in the trial will continue to receive treatment and is currently attempting to identify new funding to allocate to complete the ODAK trial.

4 Potential Impact

The ODAK project intends to improve the lives of people affected by Acanthamoeba Keratitis (AK), a rare ocular disease ultimately leading to blindness if not adequately cured. This project has identified the safest and most effective polyexamethylene biguanide (PHMB) eye drop product for treating patients with AK. The ODAK Consortium had planned to complete the Phase III clinical study and apply for marketing authorisation before project end but, due to unforeseen delays caused by the takeover of the pharmaceutical company supplying PHMB, the project was behind schedule and unable to complete these goals. The ODAK Consortium recognised that a project extension was needed, to use the allocated FP7 funds for the clinical study. A no-cost project extension request to the EC for completing patient recruitment was refused by the EC project managers. This leaves a large funding gap to complete the trial. The lead ODAK partner SIFI, who is the Trial Sponsor, is now in the process of raising funds to complete the study. The project is within touching distance of success.

ODAK work to date has very significantly advanced the preclinical and clinical work on PHMB and removed the main research and development barriers for the Market Authorisation (MA) of PHMB. This project will significantly advance the launch of the first authorised drug treatment for AK.

At the end the ODAK project major progress had been made towards:

- A safe and effective drug for AK
- A new gold standard of care for AK patients in Europe
- Accelerating patient access to both 1 and 2
- Awareness raising of the disease in Europe including through public advice information, patient specific information and support materials.
- Raised awareness amongst a global clinical community about the disease and problems with misdiagnosis – this aims to reduce the delays in AK diagnosis.

The personal impact of an effective treatment of AK will be significant in terms of health, independence, activities of daily living and quality of life. Family and friends obviously will also benefit, as their lives will be less affected by the need to support the AK patient. The new ODAK drug will reduce the burden on healthcare providers and societal of this disease.



4.1.1 Scientific Impact

AK is a rare eye disease with no licensed treatment. A survey by ODAK of over 60 clinicians and industry representatives has confirmed current AK therapies are varied depending on geographical location, drug availability and experience of the healthcare provider. In the EU anti-amoebic drugs are known to have some success in treatment but have been used off-label, with variable concentrations and treatment regimens based on empirical knowledge.

The ODAK project made significant progress in developing a treatment for AK. A retrospective study successfully confirmed the suitability of PHMB as a monotherapy, and highlighted 0.02% PHMB as the most frequently used concentration. Formulation studies were conducted to ensure PHMB eye-drops could be used as a preservative free treatment, and developed for use in a range of preclinical and clinical studies to select the most safe and effective treatment for AK. These studies confirmed 0.08% PHMB was the most effective treatment, a concentration that ophthalmologists had not considered previously, due to a lack of information on the safety of PHMB. This discovery alone will have a major impact on future successful treatment of AK and has led to the development of a new standard of care. This will be presented (by publication) to the clinical community once sufficient evidence is collected from the on-going clinical trial, see below. This will be proposed to the clinical community once sufficient evidence is collected from the on-going clinical trial, see below.

Evidence for marketing authorisation is being collected from the ongoing Phase III clinical study, due to end 2019. This trial had already recruited 24 AK patients by January 2018 (18% recruited), at the open sites. The project was refused access to the unspent EC funding needed to complete the trial, the positive impact of the interim clinical result will depend on the capability of SIFI to complete the trial and subsequent marketing authorisation application. To reduce costs further sites will not now be opened. The Phase III study is also advancing the general knowledge base on AK, the need for timely diagnosis, and the effectiveness of PHMB. These findings will be made available through:

- new information about the action and efficacy of PHMB eye-drops as a monotherapy;
- new information on current clinical practice collected and used, in combination with our PHMB safety data to develop updated “gold standard” treatment advice for clinicians.

The ODAK project aimed to produce guidelines for an optimised therapy regimen, which will be exploited by clinicians and used to improve treatment regimens for this disease. The ODAK team aim to publish this as soon as enough patients have been through all the parts of the trial, an estimated 50 patients are required to provide sufficient evidence, this should be achieved by April 2018. This would be the first detailed protocol tested for any keratitis. Simple stop-start protocols have been published before, after completion of studies, but these have been for the initial treatment of uncomplicated cases and do not deal with the problems of pre-treatment for an incorrect diagnosis or testing the management of the different causes of a relapse. We anticipate that this protocol will address these problems in about 85% of patients (the ones excluded will be those who develop scleritis needing intervention with oral immunosuppressive drugs (12.5% of the cases at Moorfields Eye Hospital, London) and those needing therapeutic surgery (often the same group). Currently, there is a very wide variation in what is done with no good evidence basis. This study will provide essential experience in managing the disease. If completed, this would provide a proof-based treatment regimen for AK that does not currently exist, allowing better patient care.



In addition to clinical impact, the ODAK project has delivered Good Manufacturing Practice (GMP) and scale up procedures of the raw active pharmaceutical ingredient (API), PHMB. SIFI will use this API in an innovative eye drop formulation.

4.1.1.1 Societal impact

The ODAK project has successfully used a range of dissemination activities to have societal impact in a number of ways.

1) AK patients. AK is a rare infectious disease predominantly affecting contact lens wearers, in westernised countries around 90% of cases are contact lens wearers. The incidence of AK is increasing with the UK currently in an outbreak, having a four-fold increase in the incidence of cases since 2011/2 (independent data in preparation for publication). Previously estimates indicated more than 1:1,000,000 across the EU. This equates to a target patient population of 508-948 EU citizens infected by AK every year, based on 2017 estimates of 508 million inhabitants in the EU. The disease is becoming more common, in Europe and globally, in large part due to the growth in the contact lens wearing population. Completion of the ODAK Phase III trial and MAA is expected to deliver a safe effective treatment for the 5000-10,000 EU citizens unfortunate enough to be infected in the next decade alone. ODAK will deliver better “standard of care” for patients, and the provision of safety data removes clinician’s concerns over current off-label treatments that limits current dose regimens. This will improve quality of life for patients, their families and careers and providing a cost-effective treatment will reduce the burden on healthcare services and society.

Successful dissemination of results and adoption of recommended treatment protocols will result in consistent treatment that is more effective providing swifter relief for patients and reduced incidence of blindness or other adverse effects. The project data will be of immediate use to clinicians treating AK patients as orphan drug designation enables the ‘compassionate use’ of optimised formulations prior to Market Authorisation. This interim solution is already alleviating the current reliance on empirical evidence for determining therapies.

Unlike most rare diseases AK has not had an established patient support group. One has recently been established in the UK and ODAK has helped to facilitate this, through workshops and direct interactions with patients. There is also an active online community facebook groups. The lack of patient support groups is due to the nature of the disease, as an infection rather than a genetic disease, it is unpredictable, and once resolved either through successful treatment or eye enucleation reoccurrence is extremely rare so patients move on with their lives. ODAK has helped patients in the UK to meet and undertake workshops with partner MEH and patient advocates, primarily Irenie Ekkeshis who was an advisor to the ODAK project.

The ODAK project identified the need for reliable patient information, Moorfields Eye Hospital, an ODAK partner, Moorfields Eye Hospital, developed a patient information leaflet through patient workshops to provide answers for AK sufferers. This leaflet was translated and disseminated on the ODAK website into French, Italian, German, Spanish, Polish and Dutch. The patient workshops established a AK support group, the first steps to an official patient group and the ODAK team also worked with Rare Connect, an EU initiative to connect rare disease patients and provide a forum for AK patients at a global level. A series of short films of patient stories have been undertaken and disseminated via the website, YouTube and social media to highlight patient experiences.



2) Ophthalmologists and healthcare providers. Early diagnosis is essential for effective treatment of AK. In general, 50% of AK cases are misdiagnosed as herpes simplex virus. This is due to the rarity of the disease, and initial symptoms being very similar to other bacterial/fungal/viral eye infections. Incorrect diagnosis as herpes also causes problems as the standard treatment is with topical steroids which effectively feed the amoeba and can make treatment more difficult and prolonged when finally diagnosed correctly. Following consultation with AK experts, the ODAK team developed an AK awareness campaign targeting ophthalmologists at the EuCornea conference 2017 held in Lisbon, Portugal. The key message was 'Eye Infection, Contact Lens? Think AK'. This was to highlight that if a patient is a contact lens wearer with no history of herpes infection then AK should be considered. The ODAK team also conducted a AK survey of ophthalmologists attending EuCornea. The survey was completed by 63 ophthalmologists from 37 countries. 95% of those surveyed thought more training and awareness of AK was needed. It also highlighted the range of off label treatments used (more than 10, including honey) and the high rate of misdiagnosis.

3) Contact lens manufacturers. The ODAK team consulted contact lens manufacturers at conferences of the British Contact Lens Association (BCLA) with regard to highlighting the risk factors associated with AK. The ODAK project also supported Irenie Ekkeshis from the AK support group who has led the 'No Water' Campaign to highlight that AK contamination is the key infection route with lenses coming into contact with water either through bathing, swimming or water from domestic taps. Irenie won the Sheila McKechnie Health Campaigner of the Year Award 2015 and Vision Pioneer Award 2016 for her campaigns.

4) To society as a whole. ODAK has disseminated information via social media, the ODAK project website and through presentations, raising awareness of the disease and associated risk factors. This is important since AK is a preventable disease but because it is rare, few people have heard of it or appreciate the risks of AK contamination and contact lens wearing. Additional material has been prepared and dissemination activities will continue beyond the project, through print and online media. This focusses on raising awareness of the risk factors, and concerns about misdiagnosis.

Society will also benefit from potential new PHMB Drug and Antimicrobial products: cGMP PHMB manufacturing developed in the ODAK project is needed for novel pharmaceutical products to meet GMP standards in manufacturing, testing, and quality in order to ensure a safe drug product for human use. This cGMP process also provides a safe new source of PHMB that is widely used for other clinical uses including intra-operative irrigation, pre- and post-surgery skin and mucous membrane disinfection, post-operative dressings, surgical and non-surgical wound dressings, surgical bath/hydrotherapy, chronic wounds like diabetic foot ulcer and burn wound management, routine antisepsis during minor incisions, catheterization, and surface disinfection. It is also used in some veterinary products.

In new nano-pharmaceutical approaches, PHMB has been identified as an effective nano carrier for drugs and has shown potential in other nanomedicine approaches. PHMB is able to enter a wide range of cells and can be used to deliver drugs into a range of cells. Currently biotech companies and academic groups are working with PHMB polymers to generate nanoparticles for drug delivery. Other groups are investigating PHMB as an effective antimicrobial against infectious diseases e.g. cutaneous leishmaniasis (CL) that is a neglected tropical disease caused by protozoan parasites of the genus *Leishmania*. These clinical and veterinary uses are potential markets for a GMP source of PHMB.



A number of potential companies have already been identified interested in PHMB as a nanocarrier for drugs or as an effective antimicrobial and a further tool to address the global problem of Antimicrobial Resistance (AMR) to conventional antimicrobial drugs. This can contribute to the Global Action Plan on Microbial Resistance (WHO, 2015).

5) Rare Disease Community. The clinical development of PHMB, and subsequent Marketing Authorisation will deliver a new licensed drug for the rare diseases AK. This contributes to the early International Rare Diseases Research Consortium goal to deliver 200 new rare disease therapies by 2020. The project success also helps to meet the new IRDiRC Goals 2017-2027 for all patients to have access timely and accurate diagnosis, and improved care and safer therapy.

4.1.2 Dissemination activities performed

The project website (www.odak-project.eu) is designed as an effective and wide-reaching dissemination tool for the ODAK project. The homepage promotes the project identity utilising the ODAK logo and project aims while highlighting it is an FP7 EU funded project.

The project summary is provided in Italian, Spanish, French, Dutch, Polish, German as well as English by clicking on the appropriate flag. Vision impaired access to the site is also provided through a range of enlargement and screen/text colour options available for every page.

The website features latest news and events page relating to the ODAK project activities. The website has attracted a wide range of stakeholders who have an interest in AK, from clinicians looking for current information on treatment, AK patients looking for advice or clinical trials updates, to the scientific and medical community seeking technical material and the public at large. The headings are designed around the different stakeholder's interests. A menu with information relating to the aims and objectives of the project, details of the work packages and the partners involved in the project and their roles is included.

The website provides specific information on:

- The disease providing current information on incidence and cause
- Mode of Infection containing detailed technical information on how *Acanthamoeba* infection occurs
- Diagnosis detailing current methods used to diagnose AK
- Current treatments providing information aimed at clinicians and patients on current practises in AK treatment
- Advice for contact lens wearers, providing the most up to date information to inform contact lens wearers of the risk factors and how to avoid infection
- Frequently asked questions with translations into Italian, Spanish, French, Dutch, Polish, German
- Patient stories with a selection of real AK patients providing an insight into what it is like to have the disease and patient experience of current treatment and care.

The website also hosts a number of short information films. These include:

- Diagnosis of AK
- Current treatment of AK
- How common is AK
- And a range of filmed patient stories from AK sufferers



The website includes links to other websites of interest to stakeholders including vision and eye care sites, rare disease organisations and charities. Information available to download includes:

- The ODAK project brochure
- ODAK poster presentations and abstracts
- Ophthalmic magazine interview with the project director

The website will be maintained for the next two years.

Social media has been used to disseminate information on project activities through a Facebook and twitter site. Facebook is particularly useful as there two AK private groups established, an English and a Spanish group. YouTube was also utilised to host the ODAK information films.

ODAK have used press releases to highlight project activity and results including the start of the clinical trials.

ODAK project brochure. This was developed for use by all partners to give an overview of the project and relevant contact information.

ODAK Workshops: The ODAK team participated in two patient workshops held in London, UK in April 2014 and September 2016. These workshops developed a patient support network which enabled the production of a AK patient leaflet, provided patient experiences of AK, both written and on film, and reviewed the Phase III Trial Patient Information form.

Information about the trial has been listed on the orphanet web portal for rare diseases for Rare Diseases (<http://www.orpha.net/consor/cgi-bin/index.php?lng=EN>).

Information about the disease has been published by ODAK on the Rare Connect website. We have also connected the informal AK patient group members with this online portal that is designed to connect rare disease patients globally <https://www.rareconnect.org/en>.

ODAK have contacted the Genetic and Rare Diseases Information Center (GARD) at NIH and offered to supply summary information about the disease for their online rare disease information website.

4.1.3 Scientific communication

ODAK has been a highly successful project with numerous scientific results being generated. It is worth to mention that most of the project results have been published in the Investigative Ophthalmology & Visual Science (IOVS) an online journal published by the Association for Research in Vision and Ophthalmology (ARVO). With Impact Factor of 3.303 this journal is ranking sixth out of 56 ophthalmology journals in the recent Journal Citation Reports. Communication towards the scientific community was carried out by all partners involved in the ODAK project through participation – oral or poster presentations – to diverse scientific events (meetings, congresses). 16 conferences were attended including IRDiRC, ARVO, TFOS, ECRD, BCLA, EuCornea and the Royal college of Ophthalmologists. The complete list of scientific presentations is available for download from the ODAK website. The ODAK team also utilised the EuCornea congress as an exhibitor undertaking an AK survey of Ophthalmologists, raising awareness of the ODAK project, and promoting the ‘Think AK’ campaign to improve rates of diagnosis.



4.1.4 Exploitation of results

Some ODAK Partners will continue to collaborate in developing new alliances and/or funding research. In addition, regulatory assistance as well as clinical advisor available in the ODAK Consortium will be exploited beyond the end of the project. The three main exploitable results are:

PHMB as a Licensed Drug protected in EU, US and Global markets

PHMB has obtained the designation of an orphan drug and as such can benefit from 10 years of market exclusivity, one of the incentives that the European Union has activated for this type of medicine. The designation of an orphan drug is reserved for medicinal products indicated for the treatment of a chronic, debilitating or life-threatening disease, which affects less than five in 10,000 patients in the European Union. PHMB designation has been also granted in the United States of America. The technical solutions developed during the ODAK project have generated a continuous knowledge transfer from the research work done in non-clinical activities to the PHMB eye-drops development. This result will be positively utilised in the future manufacturing activities of the 0.08% PHMB eye-drops. SIFI will exploit this technical information to implement standardisation process of the manufacturing activities by ensuring an increased performance of the PHMB eye-drop product and its applicability to the actual market needs.

SIFI will commit itself in exploiting the successful results of the ODAK project to organise a well-structured dossier to be submitted for Market Authorisation Application to the European Medicine Agency. The networking activities acquired in the ODAK project will be a basic condition to expand the innovative and safe PHMB eyedrop product outside Europe. Indeed, the recent Orphan Drug Designation approval by the FDA will give the opportunity to get Marketing Authorization in USA.

The current ambition is to make PHMB available in Italy, UK and Poland under compassionate use during the clinical trial period and during the MAA approval process.

Following Market Authorisation and initial product launch in the EU it is expected that up to 800 cases will be treated each year based on literature data and best estimates. Launch in the US will open up a further 500 cases per year. Incidence data suggests that in other populated countries like China and India the potential number of new cases of AK could be around 4,000-5,000 each year. This represents a large existing global market providing important export opportunities. Product launch is expected in 2020. We expect to treat 450 patients in year 2 and 1000 patients in year 3, including non-EU countries. Initial investment is being made by SIFI, to enter global markets partnership agreements will be made with important companies in the target regions.

A new standard of care for AK

The new clinical guidelines for an optimised therapy regimen will be published Q2-3 2018. These will be adopted by clinicians. This will be the first detailed protocol tested for any keratitis and used to improve treatment regimens for AK. The protocol should address treatment needs for about 85% of patients and lead to new standard of care being adopted across the EU and more broadly by clinicians in other countries, improving patient care which has become a priority for all health care providers with the overall objective of achieving a high degree of patient satisfaction.

**A new cGMP PHMB Product for global markets:**

Following extensive searches by SIFI, Ceratium and two biotechnology SME businesses no GMP source of PHMB has been identified, from any manufacturer, anywhere in the world. The ODAK project undertook to work with a pharmaceutical manufacturer to produce the first GMP certified PHMB product for use as an active pharmaceutical ingredient (API) and potentially a source for other commercial products requiring or benefiting from PHMB under GMP status.

The availability of PHMB as a cGMP product has the potential to open new markets for SIFI, either directly or through licensed manufacturing. A number of potential companies have already been identified interested in PHMB manufactured under cGMP conditions. PHMB can be used as a nanocarrier system for delivering drugs or as an effective new antimicrobial product. In this last case, PHMB can contribute to the Global Action Plan on Microbial Resistance (WHO, 2015).

The ODAK project have already had discussions with two European companies that wish to source PHMB with GMP status. Before the Marketing Authorisation Application, 0.08% PHMB eye-drops will be produced under complete GMP conditions, assuring continuous supply of the drug product for the treatment of the AK patients, in the trial and upon request by clinicians to SIFI where logistics and regulations allow.

ODAK addresses global concerns.

During the EUCornea event in Lisbon in 2017 clinicians and industry workers were asked about the prevalence of the AK, treatment options and availability of drugs to treat the disease off-label. The results are summarised in the following info graphic. There was very positive feedback about the ambition of the ODAK project and a high level of interest in the project outcomes and potential availability of a licensed drug. Access to effective antimicrobials and a robust standard of care were seen as key barriers to allowing clinicians to undertake effective treatment.

ODAK

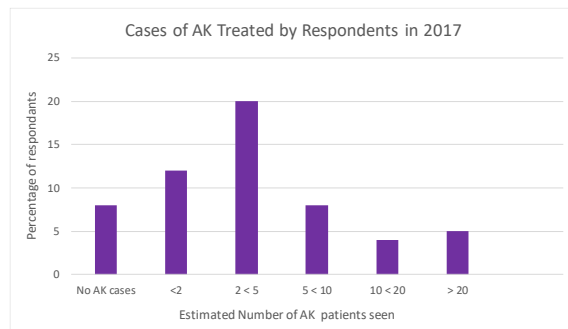
Orphan Drug for Acanthamoeba Keratitis



16 EU Countries
52% of participants



21 Non EU Countries
48% of participants

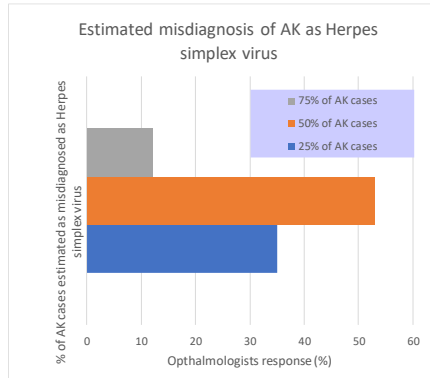
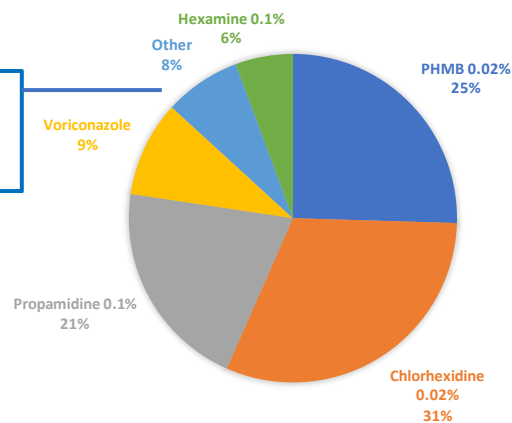


57 %

43 %

84% requested to be added to the ODAK mailing list to be kept informed of the ODAK project progress

- Honey
- Amphotericin B
- Desomedina
- Fluconazole
- Cross linking



IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

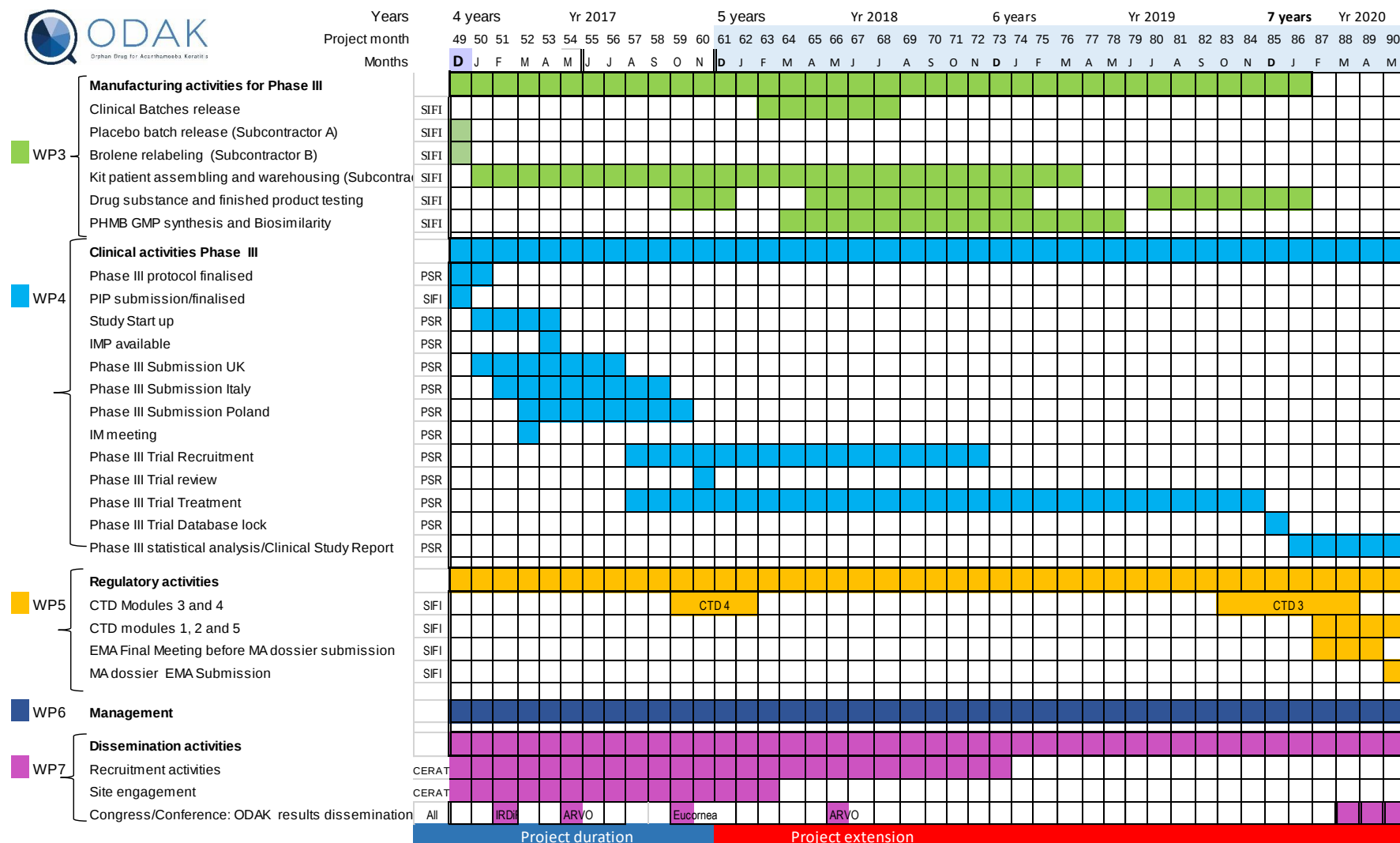
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- PHMB will be the first approved therapy for this rare disease
- ODAK will improve training to reduce misdiagnosis
- ODAK will develop a gold standard of care

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Gantt – Amendment request 1 (30-month extension)





Gantt – Amendment request 2 (12-month extension)

