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Keywords:	Cleft Palate, Clinical Trial, Cleft Lip, Histology

A phase I-IIa clinical trial to evaluate the safety, feasibility, and efficacy of the use of a palate mucosa generated by tissue engineering for the treatment of cleft palate children: the BIOCLEFT study protocol

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ABSTRACT

Introduction. Current gold-standard treatment for orofacial cleft (OFC) patients is the surgical repair of the palatal defect (uranostaphylorrhaphy), which is associated to growth defects and hypoplasia of the maxillofacial structures. This study will analyze the potential of a bioengineered model of artificial palate mucosa generated by tissue engineering using autologous stromal and epithelial cells and nanostructured fibrin-agarose biomaterials to improve the results of the treatment of OFC patients with unilateral cleft palate and lip.

Methods and analysis. A phase I-IIa clinical trial was implemented to determine the feasibility and biosafety of a procedure in which a bioartificial palate mucosa is grafted on the areas of denudated bone in OFC patients subjected to uranostaphylorrhaphy. Control patients will receive the standard treatment. 5 patients will be included in the first biosafety phase of the study. A second phase will be implemented with 10 patients randomly assigned to the intervention or control groups (1:1). A mucosa biopsy will be previously obtained from each patient, and a bioartificial palate mucosa will be fabricated as an advanced therapy medicinal product. The intervention group will receive standard treatment followed by application of this autologous product. Feasibility will be analyzed at the moment of surgery. 9 postimplant visits are scheduled in a 2-year follow-up period, in which local and systemic biosafety will be analyzed by determining the evolution of the graft (signs of necrosis, rejection, inflammation, etc.) and the patient. Preliminary signs of efficiency will be also explored by sequentially evaluating cranio-maxillo-facial development, hearing impairment, speech capability and the quality of life of the family.

Ethics and dissemination. The study was approved by the Committee of Ethics in Research with Medicinal Products (CEIm) and authorized by the Spanish Medicines Agency (AEMPS). Results of the study will be published in peer-reviewed journals.

Trial registration. ClinicalTrials.gov: NCT06408337; Euclinicaltrials.eu: 2023-506913-23-00.

KEYWORDS

Cleft palate, Cleft lip, Histology, Clinical trial

ARTICLE SUMMARY

Strengths and limitations of this study:

⇒ The study is one of the few trials evaluating an advanced therapy medicinal product approved by the Spanish Medicines Agency in children.

⇒ This is the first clinical trial in which a bioartificial palate mucosa generated by tissue engineering will be applied to children born with orofacial cleft.

⇒ Single-center design could limit the extrapolation of the results.

⇒ The sample size of 15 patients is reduced, although it could be sufficient for an initial feasibility and biosafety analysis.

INTRODUCTION

The embryonic development of the tissues conforming the human maxillofacial structures is very complex and depends on a large number of genes whose expression must be finely regulated by a network of genetic, environmental and micro-RNA factors (Schoen et al., 2017; Suzuki et al., 2018). Disruption or dysregulation of these factors can lead to a congenital defect called orofacial cleft (OFC), which has been reported to affect 1:700 to 1:1000 live births, being the most common congenital defect in developed countries, only after Down syndrome (Nasreddine et al., 2021). OFC may affect the patient's lip, palate or both structures, and it can be clinically detected at birth as a lack of fusion of the different maxillofacial processes, resulting in a defect in the lip and/or the palate hard and soft tissues (Robinson et al., 2024). This condition is normally associated with serious physical, psychological and social alterations affecting the patients and their families (Ueki et al., 2019), as a consequence of the primary malformation, but also due to the complex surgical interventions and interdisciplinary medical-surgical treatments that will be necessary for the clinical management of the patients (Kumar et al., 2020; van Roey et al., 2024). Typically, management is long and complex and includes, among others, surgical corrections, orthodontic treatments, bone grafts, rhinoplasty, psychotherapy and speech therapy treatments (Kumar et al., 2020), and the final results of the standard treatments are not always optimal (Boot and Winters, 2024). In fact, the gold-standard surgical treatment applied to palatal repair is uranostaphylorrhaphy, which is based on the use of mucosal flaps obtained from the remaining areas of the hard palate, that are sutured in the midline to generate a physical barrier between the oral and the nasal cavities (Tavakolinejad et al., 2014). Unfortunately, this procedure is normally associated to maxillofacial growth impairment and hypoplasia of the craniofacial structures, with disturbance of facial growth, as a consequence of the denudation generated at the palate bone, and the development alterations derived from this denuded bone (De La Pedraja et al., 2000; Antoneli et al., 2023). In cases affected by cleft lip and palate, the lip is normally repaired (cheiloplasty) when the patient is 3 to 6 months old, whereas the palate is usually subjected to surgical repair in patients around approximately one year later, when the patient is approximately 18 months old (Lendt et al., 2024).

One of the possible treatment alternatives is the use of bioartificial tissues generated by tissue engineering (TE). TE combines live cells with biocompatible biomaterials and growth factors to generate functional tissue substitutes able to replace damaged tissues and organs (Langer and Vacanti, 1993). In the field of OFC, only a few models of bioartificial tissues generated by TE have been described and evaluated in animal models (Natsir Kalla et al., 2024). One of these models is BIOCLEFT, a palate mucosa substitute generated by our research group using nanostructured fibrin-agarose biomaterials combined with oral mucosa stromal and epithelial cells (fibroblasts and keratinocytes, respectively). The use of nanostructured fibrin-agarose biomaterials previously showed good biocompatibility and promising clinical results in patients with severe corneal ulcers (González-Gallardo et al., 2023) and extensive skin burns (Martin-Piedra et al., 2023). Application of the this palate substitute in an animal model of palate damage in newborn rabbits resulted in a significant improvement in the development and growth of hard and soft tissues, with a positive final outcome in most animals (Fernández-Valadés-Gámez et al., 2016). After a thorough evaluation and characterization of the BIOCLEFT product at the biomechanical, histological, histochemical and immunohistochemical levels (Scionti et al., 2014; Fernández-Valadés-Gámez et al., 2016; Martín-Piedra et al., 2017), we obtained approval (date: November, 20th, 2023) by the Spanish Medicines Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS*) to generate this tissue substitute as an advanced therapy

medicinal product (ATMP) and to implement the BIOCLEFT clinical trial in patients affected by cleft palate.

The aim of the present work is to describe the BIOCLEFT clinical trial. This trial will determine the feasibility and biosafety of this novel TE product in children with cleft palate, and will preliminary evaluate the initial signs of efficacy of the treatment.

METHODS AND ANALYSIS

Study design

The BIOCLEFT clinical trial is a phase I-IIa controlled, open-label, randomized, unicentric advanced therapies trial whose main goal is to evaluate the feasibility and safety of an autologous palate mucosa generated by TE in cleft palate children, as compared to the gold-standard treatment in which the palate bone is not grafted with any material and is left denudated. The study will not be blinded to professionals involved in its development.

The initial phase of the clinical trial will sequentially recruit the first 5 patients enrolled in the study, and a safety period of 30 days has been established between patient and patient. These initial patients will be subjected to the gold-standard surgical procedure (uranostaphylorrhaphy) followed by grafting of the BIOCLEFT product, consisting in a palate mucosa substitute generated by TE. An interim biosafety analysis will be performed after the last patient included in this initial phase reached 1.5 months of follow-up. If the results of this analysis are positive, the study will continue with its second phase. In the event that the safety analysis determine that the product is not safe, the clinical trial will be stopped and ended.

In the second phase of the study, 10 additional cleft palate patients will be recruited and randomly assigned to one of the following groups (Figure 1):

1) Control group (5 patients). In this case, patients will receive the gold-standard uranostaphylorrhaphy treatment without application of any grafting material.

2) Intervention group (5 patients). These children will receive the gold-standard treatment followed by implant of the artificial palate mucosa, as it was the case of the patients enrolled in the initial phase of the trial. In consequence, the total number of cases corresponding to this group will be 10 (5 at the initial phase and 5 at the second phase).

The clinical trial was initiated on April, 17th, 2024. At the moment of submission of the present manuscript, the clinical trial is in the phase of recruiting the 5 patients corresponding to the initial phase of the study.

Patients and inclusion and exclusion criteria

Children with cleft palate associated to unilateral cleft lip will be included in the study.

Inclusion Criteria:

- Male or female children younger than 3 years of age.
- Patients diagnosed with non-syndromic cleft palate and unilateral cleft lip.
- Patients whose legal guardians (usually, their parents) accept the inclusion of the patients in the present clinical trial and sign the informed consent.
- Children who donated a sample of oral mucosa at the moment of the cheiloplasty, performed approximately one year earlier.

Exclusion Criteria:

- Patients diagnosed with syndromic cleft lip and/or palate.
- Patients affected by bilateral cleft lip.
- Patients whose legal guardians (usually, their parents) do not accept the inclusion of the patients in the present clinical trial or do not sign the informed consent.

- Children older than 3 years of age.
- Children with active infectious diseases, such as HIV, HBV or HCV infection.
- Children with severe hematological disorders/blood dyscrasias, hepatic or renal dysfunction/failure, endocrine disorders/dysfunctions or metabolic bone diseases (Paget's disease, hypercalcemia, etc.).
- Children with allergies or hypersensitivity to any of the components/excipients of the bioartificial tissue generated by TE.
- Children diagnosed with malignant neoplasms or other severe conditions.
- Children with cleft lip and palate who have other congenital malformations or conditions that could influence the results of the study.
- Any other situations, including medical or social reasons, that could alter the normal development of the clinical trial or the interpretation of the results.

Surgical procedure

All patients enrolled in the study correspond to children with non-syndromic cleft palate and unilateral cleft lip treated at the Craniofacial Malformations and Cleft Lip and Palate Management Unit (CMU) of the University Hospital Virgen de las Nieves of Granada, Spain. According to the management protocols available at this Unit, all these patients are first subjected to cheiloplasty surgery to repair the lip defect. At this moment, some oral mucosa biopsies are obtained and transferred to a GMP facility allocated at the Advanced Therapies Platform of the ibs.GRANADA Research Institute and the University Hospital Virgen de las Nieves of Granada, where epithelial cells (keratinocytes) and stromal cells (fibroblasts) are isolated using enzymatic digestion methods, cultured and expanded, as described previously (Fernández-Valadés-Gámez et al., 2016; Martín-Piedra et al., 2017). Cell cultures are then cryopreserved for delayed use. Then, the palatal defect is repaired by applying a modified von Langenbeck uranostaphylorrhaphy surgical technique when the patient is around 18 months old. This procedure consists in making two medial and lateral incisions at each side of the palate cleft, followed by a careful detaching of the soft tissue from the palatine bone, without altering its vascular pedicle, in order to generate a pediculated flap at each side of the palate (Peyvasteh et al., 2023). Then, both flaps are sutured together in the midline of the palate defect to generate a physical separation of the oral and the nasal cavity. To restore the velopharyngeal function, muscles are also detached and repaired using surgical sutures (Smith and Ugalde, 2009).

In the group of children assigned to the intervention group, a palate mucosa substitute generated by TE will then be surgically applied. This substitute will be generated as an ATMP at the Advanced Therapies Platform using autologous stromal and epithelial cells previously cultured from the biopsies taken at the moment of the cheiloplasty. First, a stromal layer will be fabricated using fibrin-agarose biomaterials with cultured fibroblasts within. In brief, per mL of volume, 760 µL of human plasma obtained from plasma donors will be combined with 15 µL of tranexamic acid (Amchafibrin 5 mg/mL, MEDA Pharma SL, Madrid, Spain), 100 µL of 2% agarose melted in PBS (Merck, Darmstadt, Germany), 50 µL of $CaCl_2$ at the concentration of 1% (Merck), and 75 µL of DMEM culture medium (Thermo Fisher Scientific-Gibco, Waltham, Massachusetts, USA), in which 100,000 cultured fibroblasts were previously resuspended (Blanco-Elices et al., 2023). Then, the patient's keratinocytes (100,000 cells per mL of stromal substitute) will be subcultured on top of the stromal substitute to generate an epithelial layer. The palate mucosa substitutes will be generated on porous culture inserts to promote epithelial stratification and differentiation using the air-liquid culture technique, as previously described (González-Andrades et al., 2009; Viñuela-Prieto et al., 2015). Finally, substitutes will be subjected to plastic compression nanostructuration to improve the biomechanical properties of the product, as described in previous manuscripts (Scionti et al., 2014). This palate mucosa substitute will be applied on the denudated palatine bone at both sides of the palate defect and will be fixed using resorbable suture material.

Outcomes, measures and variables of the study

The clinical trial has been designed with two preimplant visits (visits 1 and 2), a visit at the moment of the surgical repair of the palatal defect (visit 3) and 9 postimplant evaluation visits (visits 4 to 12), with the last visit held 24 months after the surgical procedure (Figure 2):

- Preimplant visits: the first visit will take place when the child is approximately 12 months old, according to current follow-up and treatment protocols applied at the CMU. At this moment, patients will be evaluated and those cases fulfilling all inclusion criteria will be selected and recruited for the study. Informed consent will be obtained at this moment. The second visit should confirm the patient's conditions for recruitment, and aleatorization will be performed to assign each participant to one of the groups of the study (control or intervention group), except for the first 5 patients, corresponding to the phase I of the trial.
- Implant visit: at the moment of the uranostaphylorrhaphy surgical repair of the palate defect (with or without implant of the bioartificial palate mucosa), the patient will be evaluated under general anesthesia. At this moment (visit 3), measures will be obtained from the patient's palate cleft. Cranio-maxillo-facial Images and palatal impressions in alginate gels will be obtained. These impressions will be then used to generate 3D mold models of the patient's defect before the surgical treatment. In addition, participants in the study will be evaluated by a pediatric otorhinolaryngologist, and tympanostomy ventilation tubes will be implanted if necessary.
- Postimplant visits. The first 2 postimplant visits will take place 24h and 48h after the surgical procedure, respectively, when the patient is still at the hospital. In these visits, the general situation of the patient will be evaluated, along with the surgical area at the palate. Specifically, the situation of the implant will be assessed, and short-term side effects and complications will be detected, including graft detachment, bleeding, necrosis, infection or other unexpected findings. Normally, the patient will be discharged from the hospital 48h after the surgical procedure. The same parameters will be analyzed during the rest of visits (visit 6 to 12), which will take place after the patient's discharge. The TAPQOL quality of life questionnaire will be used to evaluate the family of the patient at visits 7, 10 and 12, and functional evaluation of the child's speech will be carried out by a pediatric speech therapist at visit 11. Evaluation by a pediatric otorhinolaryngologist will be performed at the patient's needs, at visits 8, 9, 10 and/or 11.

As an initial clinical trial, variables that will be quantified and analyzed are mainly related to the analyses of feasibility of the procedure and biosafety of the implant. However, secondary variables related to initial efficacy will be preliminary analyzed, and the present trial will record some initial signs of efficiency of the implant. Variables that will be analyzed in this trial include:

1. Primary outcome measures.
    a. Feasibility of the procedure will be assessed using a questionnaire generated ad-hoc for this trial that includes items related to the difficulties found during the grafting process, macroscopic aspect, consistency, handling and suturability of the bioartificial palate mucosa and other factors related to the factibility of the procedure.
    b. Biosafety will be determined by analyzing the presence of serious and non-serious adverse or unexpected side events related to the implant of the artificial tissue, such as excessive bleeding, necrosis, infection, inflammation or other local or systemic reactions that could be related to the implant.
2. Secondary outcome measures.

a. Effects of the implant on the surgical site healing. Regeneration and healing of the palatine bone defect generated during the uranostaphylorrhaphy will be analyzed by evaluating the surgical site at different time points.
b. Evaluation of the aesthetic results. The aesthetic appearance of the patients' head and face will be analyzed by analyzing macroscopic photographs taken from the patient at different follow-up times. A specific aesthetic appearance assessment scale designed for OFC children will be used.
c. Preliminary evaluation of cranio-maxillo-facial growth and development. Although the follow-up time of the present clinical trial is only 24 months, initial preliminary signs of the effects of the implant on cranio-maxillo-facial growth and development will also be preliminary assessed by quantifying relevant measures and distances in the photographs and 3D molds reconstruction models obtained from the patient at different time points.
d. Hearing evaluation. Patients will be evaluated by a pediatric otorhinolaryngologist to detect any signs of hearing impairment or otologic defects at the different visits of the trial.
e. Analysis of quality of life. The family of the patients will be asked to fill out the TAPQOL questionnaire for children between 1-5 years old, in order to determine if the treatment could have an effect on improving the quality of life of families with children affected by OFC.
f. Functional evaluation by a speech therapist. An expert pediatric speech therapist will determine if the treatment has any influence on relevant speech parameters, such as the ability to pronounce vowels and consonants, nasal escape, palate mobility, swallowing and articulation of functional language.

DISCUSSION

Despite the incidence and social and healthcare relevance of OFC, current treatment of this patients is still based on surgical techniques originally described many decades ago (Naidu et al., 2022). Although these techniques allow surgeons to generate a physical barrier between the oral and nasal cavities, the final outcomes of these patients are still suboptimal (Boot and Winters, 2024), and new treatment alternatives are in need. Among the most promising alternatives, advanced therapies offer the possibility of treating patients affected by severe conditions using bioartificial tissues able to efficiently promote tissue regeneration (Diaz-Solano et al., 2024).

Artificial tissues generated as ATMP using TE strategies are increasingly demonstrating potential clinical usefulness in diverse types of complex pathologies, and their application in patients with severe diseases demonstrated to be successful and safe (Smeringaiova et al., 2021; González-Gallardo et al., 2023; Martin-Piedra et al., 2023; Gormley et al., 2024). however, the clinical translation of TE products is still very limited, and few experience is available, especially in certain pathological conditions (Joyce et al., 2023). In addition, the regulatory frame associated to the clinical translation is very complex, what makes the use of these products in humans very challenging (Sanchez-Guijo et al., 2024).

Once we had the positive experience of the successful clinical application of other human artificial tissues based on the same nanostructured fibrin-agarose biomaterials, we designed the present BIOCLEFT clinical trial (González-Gallardo et al., 2023; Martin-Piedra et al., 2023). As one of the first advanced therapies clinical trials applied to OFC patients, the present trial was designed, according to the requirements of the AEMPS,

as a phase I-IIa trial. In general, novel products, especially those corresponding to ATMP, must be initially evaluated for biosafety either in early-phase clinical trials or in the frame of hospital exemption and compassionate use (Egea-Guerrero et al., 2019; Cuende et al., 2022). In the case of the BIOCLEFT clinical trial, we obtained trial authorization from the national regulatory agency in Spain instead of applying for hospital exemption, as previously done for a previous model of artificial skin generated by the group (Egea-Guerrero et al., 2019). This will allow us to provide stronger scientific evidence of the effects of the artificial palate mucosa and will make possible the future application for a centralized marketing authorization in Europe, without the restrictive conditions associated to hospital exemption (Cuende et al., 2022).

As an early-phase clinical trial, the present study is mainly focused on determining if the implant of the artificial palate mucosa is feasible and safe for the patient. On the one hand, feasibility is important, since this is one of the few studies in which a medical product is grafted on the denudated areas of the palatine bone of patients affected by OFC and subjected to uranostaphylorrhaphy. In addition, it is the first time that an artificial tissue generated by TE containing two different cell populations (stromal and epithelial cells) will be generated as ATMP and applied to OFC patients. For these reasons, demonstrating that the study is physically achievable is one of the main objectives of the present study. Although feasibility studies are commonly carried out in cell therapy (Ahmadvand et al., 2023), the number of works describing the feasibility of the clinical implant of a human tissue generated by TE is still low. On the other hand, safety is one of the most important requirements of new drugs and medicinal products (Christiansen and Kirkeby, 2024), and it is probably the most important requisites of bioartificial tissues generated by TE (Schuessler-Lenz et al., 2023).

Preliminary analysis of other parameters related to the clinical usefulness of the implant will also be recorded. However, due to the short follow-up period in the patients included in the present clinical trial (24 months of postimplant follow-up), it is very unlikely that the efficacy results of the BIOCLEFT study will find significant differences between the control and the intervention groups. These preliminary results could be used to design future clinical trials in more advanced phases focused on determining the clinical efficacy of the palate mucosa substitute generated by TE.

Regarding the analysis methods used in the present study, biosafety will be analyzed by examining the patient surgical site and by evaluating the general situation and clinical parameters of the patient. Based on our previous experience with other bioartificial tissues generated by TE (González-Gallardo et al., 2023; Martin-Piedra et al., 2023), these analyses should be able to efficiently detect any possible side effects and complications of the implant, both at the short and the long term, especially due to the fact that nanostructured fibrin-agarose artificial tissues previously generated by the research group typically shows complete *in vivo* biointegration after approximately one to three months (Campos et al., 2020; Martin-Piedra et al., 2023). For the preliminary analyses of efficacy of the bioengineered product, a combination of methods will be applied, including the analysis of growth and development of the cranio-maxillo-facial structures, assessment of the hearing capability of the patient using otorhinolaryngology evaluation, analysis of the speech capability and the use of a normalized questionnaire previously used to evaluate que quality of life of children and their families (Msall, 2005). This array of evaluation methods will probably provide researchers with a preliminary idea of the functional effects of the implant on the patient, and will give us an idea on the possible positive effects of the therapy, that should be confirmed by further analyses.

The BIOCLEFT clinical trial has several limitations. On the one hand, the study will be performed using a limited number of participants, which is typically associated to lower statistical power of the results (Giner-Sorolla et al., 2024). However, for an initial biosafety study, a short sample size is commonly utilized, especially in ATMP studies. On the other hand, the follow-up period in which the patients will be followed could not

be enough to identify the beneficial effects of the implant on the patient's cranio-maxillo-facial growth, development and aesthetic appearance. If the present study is able to demonstrate that the implant is feasible and safe for the patient, future clinical trials in advanced phases should be carried out using longer follow-up periods able to allow the patient cranio-maxillo-facial structures to grow and develop.

ETHICS AND DISSEMINATION

The study was approved by the Committee of Ethics in Research with Medicinal Products (CEIm), reference FIB-BIO-2023-03 (date of approval, November 16th, 2023). As an advanced therapy study, the BIOCLEFT clinical trial was authorized by the Spanish Medicines Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS*), reference 2023-506913-23-00/ID:10008 (date of approval, November 21st, 2023). The study is performed in compliance with the Declaration of Helsinki and the principles of Good Clinical Practice. All patients' legal guardians will sign an informed consent before study entry. This clinical trial was registered at ClinicalTrials.gov with the registration number: NCT06408337. Results of the clinical trial will be published in peer-reviewed journals.

AUTHOR CONTRIBUTIONS

The study was conceived and designed by AEL, RFV, EC, BQ, EA, GC and MA. The clinical trial is being conducted by all authors, with AEL, RFV, AMP, DV and ELL participating in the surgical procedures, IG, MAMP, VC, FC, JCA, ODGG, DSP, PAF, MEE, AC and MA participating in the design and quality control of the medicinal product evaluated in the present work, and AEL, RFV, EC, BQ, EA, GC and MA participating in the generation of the documents and protocols required for the clinical trial. AEL, RFV and MA wrote the first version of the manuscript. IG, MAMP, VC and AC revised the manuscript and provided valuable information. All authors read and approved the final manuscript.

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COMPETING INTERESTS

None declared.

DATA STATEMENT

The study has been registered in ClinicalTrials.gov (NCT06408337) and Euclinicaltrials.eu (2023-506913-23-00).

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

PATIENT CONSENT FOR PUBLICATION

Not applicable.

FIGURE LEGENDS

Figure 1. Design of the BIOCLEFT clinical trial. The different phases and groups of patients are represented at each stage of the trial.

Figure 2. Stages of the BIOCLEFT clinical trial and studies that will be carried out in each visit. The moment when each visit will be programmed is shown at the left of the visit number, and the analyses that will be carried out are represented with symbols (explained below the figure). PS: post-surgery.

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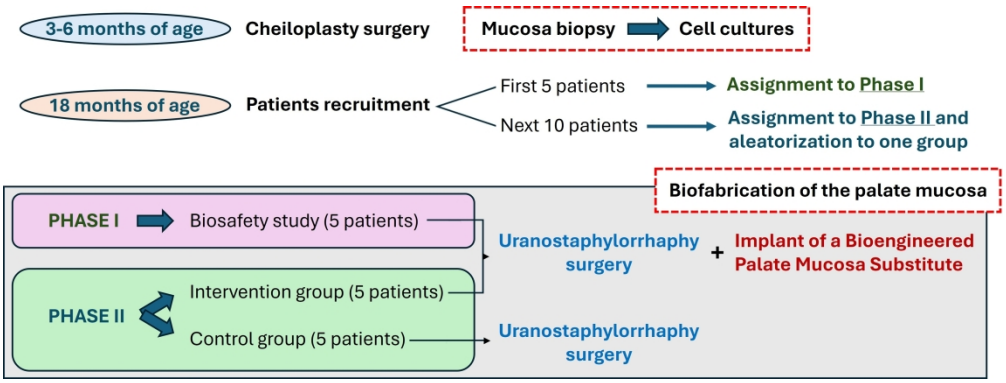

Figure 1

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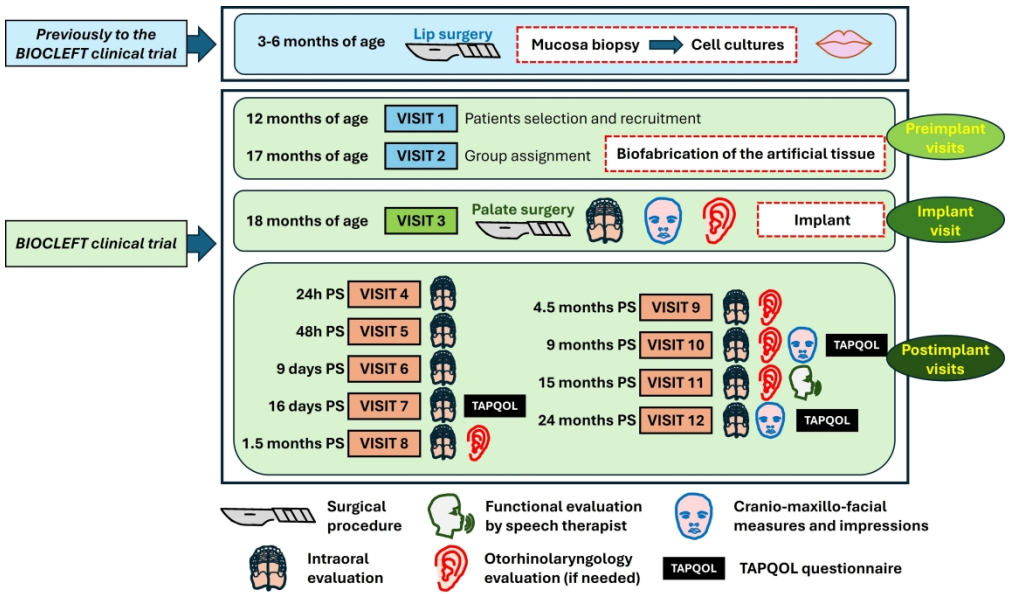

Figure 2

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A phase I-IIa clinical trial to evaluate the safety, feasibility, and efficacy of the use of a palate mucosa generated by tissue engineering for the treatment of children with cleft palate: the BIOCLEFT study protocol

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ABSTRACT

Introduction. The current gold standard treatment for patients with orofacial clefts is surgical repair of the palatal defect (uranostaphylorrhaphy), which is associated with growth defects and hypoplasia of the maxillofacial structures. This trial aims to evaluate the potential of a bioengineered artificial palate mucosa, created through tissue engineering with autologous stromal and epithelial cells and nanostructured fibrin-agarose biomaterials, to enhance treatment outcomes for patients with unilateral cleft lip and palate.

Methods and analysis. This phase I-IIa clinical trial aims to evaluate the feasibility and biosafety of a procedure involving grafting bioartificial palate mucosa onto the areas of denudated bone in patients undergoing uranostaphylorrhaphy. The control patients will undergo standard surgical treatment. Five patients will be included in the first biosafety phase. In the second phase, 10 patients will be randomly assigned to the intervention or control group (1:1). The intervention group will undergo standard surgical treatment followed by the application of autologous bioartificial palate mucosa. Feasibility will be analyzed at the time of surgery. Nine postimplant visits will be scheduled over a 2-year follow-up period, in which local and systemic biosafety will be investigated by determining graft evolution, including signs of necrosis, rejection, inflammation and patient factors. Preliminary signs of efficiency will be explored by sequentially evaluating craniomaxillofacial development, hearing impairment, speech capability, and quality of life of the family. The research will be published in journals and posted in the relevant repositories when available.

Ethics and dissemination. This study has been approved by the Committee of Ethics in Research with Medicinal Products (CEIm) and authorized by the Spanish Medicines Agency (AEMPS). The results of this study will be published in peer-reviewed journals.

Trial registration. ClinicalTrials.gov: NCT06408337; EuclinicalTrials. eu: 2023-506913-23-00.

KEYWORDS

Cleft palate, Cleft lip, Clinical trial, Histology

ARTICLE SUMMARY

Strengths and limitations of this study:

⇒ This study is one of the few trials evaluating an advanced therapeutic medicinal product approved by the Spanish Medicines Agency in children.

⇒ This is the first clinical trial that will assess the feasibility and biosafety of a tissue-engineered, bioartificial palate mucosa for treating children born with orofacial cleft.

⇒ The single-center design could limit the extrapolation of the results.

⇒ The sample size of 15 patients is small, although it could be sufficient for an initial feasibility and biosafety analysis.

INTRODUCTION

Orofacial cleft (OFC) is a congenital defect that affects 1:700 to 1:1000 live births and is the most common congenital defect in developed countries, after only Down syndrome [2]. This condition may affect the patient's lip, palate, or both structures and is usually clinically detected at birth when the different maxillofacial processes are unfused, manifesting as a defect in the lip or hard palate and soft tissues [1]. Orofacial cleft is associated with serious physical, psychological, and social impacts affecting patients and their families [3]. Aside from the primary malformation, patients and their families must also contend with complex surgical interventions and interdisciplinary medical-surgical treatments [4,5]. Typically, management is long and complex and includes surgical corrections, orthodontic treatments, bone grafts, rhinoplasty, psychotherapy, and speech therapy [4]. Moreover, the outcomes of the standard treatments are not always optimal [6].

The gold standard surgical treatment for palatal repair is uranostaphylorrhaphy, which involves obtaining mucosal flaps from the remaining areas of the hard palate and suturing the flaps in the midline to generate a physical barrier between the oral and nasal cavities [7]. Unfortunately, this procedure is associated with impaired maxillofacial growth and hypoplasia of the craniofacial structures. The denudation of the palatal bone disrupts facial growth and development [8,9]. In contrast, other surgical techniques, such as Furlow palatoplasty, which is a buccal myomucosal flap procedure, reportedly offer improved results with fewer impacts on maxillary bone growth in certain patients [10]. In patients with cleft lip and palate, the lip is routinely repaired (cheiloplasty) when the patient is 3–6 months old, whereas the palate is usually repaired surgically approximately one year later when the patient is 15–18 months old [11].

Bioartificial tissues generated by tissue engineering (TE) have been proposed to improve outcomes following surgical repair of OFC. Tissue engineering combines live cells with biocompatible biomaterials and growth factors to generate functional tissue substitutes to replace damaged tissues and organs [12]. In OFC, only a few models of bioartificial tissues generated by TE have been described and evaluated in animal models [13]. One such model is BIOCLEFT, a palatal mucosa substitute generated by our research group using nanostructured fibrin–agarose biomaterials combined with oral mucosal stromal and epithelial cells, including fibroblasts and keratinocytes. Nanostructured fibrin–agarose biomaterials have shown good biocompatibility and promising clinical results in patients with severe corneal ulcers [14] and extensive skin burns [15]. The application of this palate substitute in an animal model of palate damage in newborn rabbits resulted in significant improvement in the development and growth of hard and soft tissues, with a positive outcome in most animals [16]. After a thorough evaluation and characterization of the BIOCLEFT product at the biomechanical, histological, histochemical and immunohistochemical levels [16–18], we obtained approval (date: November, 20th, 2023) from the Spanish Medicines Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS*) to generate BIOCLEFT as an advanced therapy medicinal product (ATMP) and to implement the BIOCLEFT clinical trial in patients affected by cleft palate.

Here, we present the protocol for the phase I-IIa BIOCLEFT clinical trial (protocol version 2, date of approval: October, 19th, 2023. This trial will determine the feasibility and biosafety of this novel TE product in children with cleft palate and will preliminarily evaluate treatment efficacy.

METHODS AND ANALYSIS

Study design

The BIOCLEFT clinical trial will be a phase I-IIa controlled, open-label, randomized, unicentric advanced therapy trial to evaluate the feasibility and safety of an autologous palate mucosa substitute generated by TE in children with cleft palate. The trial coordinator is Dr. Ricardo Fernández-Valadés, and the project principal investigator is Dr. Miguel Alaminos. The sponsor is the Andalusian Network for Design and Translation of Advanced Therapies and FIBAO foundation.

The control group will undergo the gold-standard surgical repair procedure, uranostaphylorrhaphy. In contrast, the study group will be treated with the same procedure, followed by the implantation of a BIOCLEFT substitute used to cover the lateral areas of denudated bone. The professionals involved in the trial will not be blinded to the study.

The uranostaphylorrhaphy procedure used in both groups of patients consists of the closure of the central cleft by suturing the edges of the cleft together. First, the soft tissue (palate mucosa) is carefully detached from the subjacent palate bone on both sides of the palatal defect, taking care not to damage the vascular supply of the soft tissue. The right and left tissues are drawn toward the midline defect and sutured together using silk stitches. This procedure allows a physical barrier to form between the oral and nasal cavities using the palate mucosa; however, the palate bone is left denudated on both sides of the palate grafts. Finally, the uvula, soft palate, and faringopalatine muscles are repaired and sutured to reestablish the normal anatomy of the human pharynx structures.

The first five patients will be sequentially recruited in the initial phase of the clinical trial. As an early phase clinical trial, a safety period of 30 days was established between patients to ensure that the previous patient did not experience any adverse effects due to the implant before subjecting the next patient to the implant. This safety period is a common requirement of national medicine agencies for novel products whose biosafety levels have yet to be determined [19]. The Independent Data Security and Monitoring Committee will perform an interim biosafety analysis after the last patient included in the initial phase reaches 1.5 months of follow-up. This committee consists of 5 members that are independent from the sponsor and are free from any competing interests. If the safety analysis reports that the product is safe, the trial will continue to the second phase. Otherwise, the clinical trial will be terminated.

In the second phase, 10 additional patients with cleft palate will be recruited and randomly assigned to one of the following groups (Figure 1):

1) Control group (n=5), these patients will receive the gold-standard uranostaphylorrhaphy treatment without applying any grafting material.

2) Intervention group (n=5). These children will receive the gold-standard treatment, followed by implantation of the BIOCLEFT artificial palate mucosa, as is the case for patients in the initial phase of the trial. Consequently, this group's total number of patients will be 10 (five in the initial phase and five in the second phase).

This clinical trial was initiated on April 17, 2024. At the time of submission of the present protocol, the clinical trial was in the phase of recruiting five patients for the initial phase of the trial.

Patients and inclusion and exclusion criteria

Children with cleft palate, specifically unilateral cleft lip, will be included in this study. Patients will be recruited at the age of 10–14 months following the cheiloplasty procedure. As described in the Surgical Procedure section, all patients with nonsyndromic cleft palate and unilateral cleft lip will donate a small oral mucosa sample during cheiloplasty. This sample corresponds to the tissue that is usually discarded after cheiloplasty.

Inclusion criteria:

- Pediatric patients, of both genders.
- Diagnosis of total unilateral nonsyndromic cleft lip and palate (FLPNS) that will undergo surgery for correction.
- Children who have previously donated a sample of oral mucosa during the cleft lip repair procedure (cheiloplasty).
- Informed consent signed by one or both parents (or legal guardian) adequately informed of the study and willing to follow the trial procedures and instructions.

Exclusion criteria:

- Active infectious diseases.
- Allergies or hypersensitivity to any of the components or excipients of the investigational product.
- Severe hematological disorders/blood dyscrasias.
- Severe hepatic or renal dysfunction/failure.
- Serious endocrine disorders/dysfunctions.
- Malignant neoplasms.
- Active HIV, HBV, or HCV infection.
- Metabolic bone diseases (Paget's disease, hypercalcemia, etc.).
- Children with cleft lip and palate who present other congenital malformations that, in the researcher's opinion, could affect the outcomes of the trial or the interpretation of results.
- In the opinion of the investigator, any other pathologies that should not be included in the trial for medical or social reasons.

Surgical procedure

All patients enrolled in the study will be treated at the Craniofacial Malformations and Cleft Lip and Palate Management Unit (CMU) of the University Hospital Virgen de las Nieves of Granada, Spain. According to the unit's management protocols, all patients will first undergo cheiloplasty to repair the lip defect. During cheiloplasty, oral mucosal biopsies will be obtained and transferred to a Good Manufacturing Practice (GMP) facility located at the Advanced Therapies Platform of the ibs.GRANADA Research Institute and the University Hospital Virgen de las Nieves of Granada, coordinated by the Andalusian Network for the Design and Translation of Advanced Therapies. From these biopsies, epithelial cells (keratinocytes) and stromal cells (fibroblasts) will be isolated using enzymatic digestion methods, cultured, and expanded as described previously [16,18]. The cell cultures will be cryopreserved for delayed use.

The palatal defect will be repaired in all patients by applying a modified von Langenbeck uranostaphylorrhaphy surgical technique when the patient is approximately 14–18 months old. This procedure involves making two medial and lateral incisions at each side of the palatal cleft, followed by careful detachment of the soft tissue from the palatine bone without damaging its vascular pedicle, to generate a pediculated flap on each side of the palate [20]. Both flaps are then sutured together in the midline of the palate defect to physically separate the oral and nasal cavities. To maintain velopharyngeal function, the muscles are also detached and repaired using sutures [21].

For children in the intervention group, a BIOCLEFT palate mucosa substitute generated by TE will then be surgically applied to cover the denudated areas of the palatine bone on both sides of the hard palate that were exposed during the von Langenbeck surgery. BIOCLEFT will be generated as an ATMP at the Advanced Therapies Platform using autologous stromal and epithelial cells previously cultured from the biopsies taken during cheiloplasty. First, a stromal layer is fabricated using fibrin-agarose biomaterials with cultured fibroblasts. In brief, per mL of volume, 760 µL of human plasma obtained from plasma donors will be combined with 15 µL of tranexamic acid (Amchafibrin 5 mg/mL, Rotapharm, Monza, Italy), 100 µL of 2% agarose melted in phosphate-buffered solution (PBS) (Merck, Darmstadt, Germany), 50 µL of $CaCl_2$ at a concentration of 1% (Braun,

Kronberg, Germany), and 75 µL of Dulbecco's modified eagle medium (Merck) [22]. The patient's keratinocytes (100,000 cells/mL of stromal substitute) will be subcultured on top of the stromal substitute to generate an epithelial layer. Palate mucosa substitutes are generated on porous culture inserts to promote epithelial stratification and differentiation using the air–liquid culture technique as previously described [23,24]. Finally, the substitutes are subjected to plastic compression nanostructures to improve the biomechanical properties of the product, as described in previous studies [17]. This palate mucosa substitute will be applied to the denudated palatine bone on both sides of the palate defect and fixed using resorbable suture material.

Outcomes, measures, and variables

The clinical trial was designed with two preimplant visits (visits 1 and 2), one visit at the time of surgical repair of the palatal defect (visit 3), and nine postimplant evaluation visits (visits 4–12), with the last visit 24 months after uranostaphylorrhaphy (Figure 2).

- Preimplant visits: The first visit will occur when the child is approximately 12 months old (range, 10–14 months) according to the current follow-up and treatment protocols applied at the CMU. Patients will be evaluated at this visit, and patients satisfying all the inclusion criteria will be selected and recruited for the trial. Informed consent will be obtained from all the parents or caregivers of the patients. The second visit will confirm the patient's suitability for recruitment, and each patient will be randomly assigned to either the control or intervention group. The first five patients who meet the inclusion criteria will be assigned to phase I of the trial. The second visit will occur when the patient is 13–17 months old, approximately 30 days before uranostaphylorrhaphy.
- Implant visit (14–18 months of age): At the time of uranostaphylorrhaphy, with or without implantation of BIOCLEFT), the patient will be evaluated under general anesthesia. Before uranostaphylorrhaphy, the patient's palate cleft will be measured. The patient's head, face, mouth, and palate (craniomaxillofacial images) will be photographed, and palatal impressions in alginate gels will be obtained. These impressions will be used to generate 3D models of the patient's defects before surgical treatment. In addition, participants will be evaluated by a pediatric otorhinolaryngologist, and tympanostomy ventilation tubes will be implanted if necessary.
- Postimplant visits. The first two postimplant visits will occur 24 h and 48 h after uranostaphylorrhaphy when the patient is still at the hospital. During these visits, the patient's general condition and the surgical area of the palate will be evaluated. Specifically, the placement of the implant will be assessed, and short-term side effects and complications will be monitored, including graft detachment, bleeding, necrosis, infection, and other unexpected findings. Patients are routinely discharged 48h after surgery. The same parameters will be evaluated during the rest of the visits (visits 6 to 12), which will occur at 9 and 16 days and at 1.5, 4.5, 9, 15, and 24 months after discharge. The TNO-AZL Preschool Quality of Life (TAPQOL) questionnaire will be used to evaluate the patient's family at visits 7, 10, and 12, and a functional evaluation of the child's speech will be performed by a pediatric speech therapist at visit 11. If necessary, a pediatric otorhinolaryngologist will evaluate the patient at visits 8, 9, 10, 11, or 12.

As an initial clinical trial, the variables to be analyzed are mainly related to the feasibility of the procedure and the biosafety of the implant. However, secondary variables related to initial efficacy will be preliminarily analyzed, and the present trial will record some initial signs of implant efficiency. The following variables will be analyzed:

1. Primary outcome measures.
    a. Feasibility will be assessed using a questionnaire generated ad hoc for this trial that includes items related to the difficulties encountered during

the grafting process, macroscopic aspects, consistency, handling, and suturability of BIOCLEFT and other factors associated with the feasibility of the procedure (Supplementary Material S1).

b. Biosafety will be determined by analyzing the occurrence of serious and mild adverse or unexpected side events related to the implantation of BIOCLEFT, such as excessive bleeding, necrosis, infection, inflammation, or other local or systemic reactions that could be related to the implant.

2. Secondary outcome measures.

a. Effects of the implants on surgical site healing. The regeneration and healing of the palatine bone defects generated during uranostaphylorrhaphy will be analyzed by evaluating the surgical site at different time points.

b. Evaluation of aesthetic results. The appearance of the patient's head and face will be assessed by analyzing macroscopic photographs taken at different follow-up times. A specific aesthetic appearance assessment scale designed for children with OFC (Supplementary Material S2) will be used. This scale was designed based on previous scales used in children with cleft palate [25,26].

c. Preliminary evaluation of cranio-maxillofacial growth and development. Although the follow-up time of the present clinical trial is only 24 months, initial preliminary signs of the effects of the implant on craniomaxillofacial growth and development will be assessed by quantifying relevant measures and distances in the photographs and 3D models obtained from the patient at different time points.

d. Hearing evaluation. A pediatric otorhinolaryngologist will evaluate patients to detect any signs of hearing impairment or otologic defects. Once the otorhinolaryngologist has performed the initial hearing evaluation (preimplant visits), the need for follow-up postimplant visits will be assessed depending on whether the patient has any pathology.

e. Analysis of quality of life. The patients' families will be asked to fill out the TAPQOL questionnaire for children aged 1–5 years to determine if the treatment improved the quality of life of the patients' families. This questionnaire is widely used to analyze children's quality of life and contains several items evaluating 12 aspects of children's life, including sleeping, appetite, lungs, stomach, skin, motor functioning, communication, social functioning, behavioral problems, anxiety, positive mood, and liveliness [27,28].

f. Functional evaluation by a speech therapist. An expert pediatric speech therapist will determine whether the treatment influenced any relevant speech parameters, such as the ability to pronounce vowels and consonants, nasal escape, palate mobility, swallowing, and articulation of functional language. For this purpose, a 2–3 min conversational speech sample will be tape-recorded for further analysis, followed by a single-word articulation test to assess specific sounds. These tests evaluate the patient's ability to articulate speech and the resonance patterns associated with speech (hypernasality, resonance of specific vowels and consonants, detection of articulation errors).

After the trial, patients will be follow-up and treated in the CMU following the standard protocols established in this Unit.

Data sharing and diffusion plan

The results obtained from this trial will be posted in public databases and repositories as soon as possible as part of the study's data management plan. The results will be

published in a specialized journal. Personal data and those subject to special ethical or legal issues will be protected and not published. The data management plan is provided in Supplementary Material S3.

DISCUSSION

Despite the social and healthcare relevance of OFC, current treatments are still based on surgical techniques originally described many decades ago [29]. Although these techniques allow surgeons to generate a physical barrier between the oral and nasal cavities, the final outcomes of these patients remain suboptimal [6], and new treatments are needed. Among the most promising alternatives are advanced therapies using bioartificial tissues that offer the possibility of promoting tissue regeneration in patients with severe conditions [30].

Artificial tissues generated as ATMPs using TE increasingly demonstrate their potential clinical usefulness in diverse, complex pathologies. Moreover, artificial tissues have been successfully and safely used to treat patients with severe diseases [14,15,31,32]. However, the clinical translation of TE products is still limited, and little experience is available, especially for specific pathological conditions [33]. In addition, the regulatory frameworks associated with clinical translation are very complex, making using these products in humans challenging [34].

Following the successful clinical application of other human artificial tissues based on the same nanostructured fibrin–agarose biomaterials, we designed the present BIOCLEFT clinical trial [14,15]. As one of the first advanced therapy clinical trials applied to patients with OFC, the present trial was designed according to the requirements of the AEMPS as a phase I-IIa trial. In general, novel products, especially ATMPs, must be initially evaluated for biosafety, either in early-phase clinical trials or in the framework of hospital exemption and compassionate use [35,36]. For the BIOCLEFT clinical trial, we obtained authorization from the national regulatory agency in Spain instead of applying for hospital exemptions, as was done for a previous model of artificial skin generated by the group [35]. This will provide stronger scientific evidence of the effects of the artificial palate mucosa and enable future centralized marketing authorization in Europe without the restrictive conditions associated with hospital exemption [36].

As an early-phase clinical trial, the present study mainly focuses on establishing the feasibility of implanting the artificial palate mucosa and determining patient safety. Establishing feasibility is essential because the BIOCLEFT medical product is grafted onto the denudated areas of the palatine bone of patients affected by OFC during uranostaphylorrhaphy. Additionally, this is the first artificial tissue generated by TE containing two different cell populations (stromal and epithelial cells) generated as an ATMP and applied to patients with OFC. Therefore, this study primarily aims to demonstrate that the method and product are practically achievable. Although feasibility studies are common in cell therapy [37], few studies have described the feasibility of using human tissue generated by TW in clinical settings. Moreover, safety is among the most important requirements of new drugs and medicinal products [38], especially bioartificial tissues generated by TE [39].

This trial will also preliminarily analyze other parameters related to the clinical utility of the implant. However, given the short follow-up period in the present clinical trial (24 months post-implant follow-up), the efficacy between the control and intervention groups is unlikely to differ significantly. These preliminary results could be used to design future clinical trials in more advanced phases focused on determining the clinical efficacy of the palate mucosa substitutes generated by TE.

Regarding the analysis, biosafety will be analyzed by examining the patient's surgical site and evaluating the patient's general situation and clinical parameters. Based on our

previous experiences with other bioartificial tissues generated by TE [14,15], these analyses should be able to detect any possible side effects and complications effectively, both in the short and long term. Notably, the nanostructured fibrin–agarose artificial tissues previously generated by our research group typically show complete in vivo biointegration after one to three months [15,40]. To assess the preliminary efficacy of the bioengineered product, we will use a combination of methods, including analyzing the growth and development of the craniomaxillofacial structures, assessing the hearing ability of patients using otorhinolaryngology evaluation, analyzing speech ability, and using an established normalised questionnaire to evaluate the quality of life of children and their families [41]. This array of evaluation methods will provide researchers with a preliminary idea of the functional effects of the implant on the patient and will reveal the possible positive effects of the therapy, which should be confirmed by further analyses.

The BIOCLEFT clinical trial has several limitations. First, the study will be performed with a small number of participants, which is typically associated with lower statistical power [42]. However, initial biosafety studies usually include a small sample size, especially in ATMP studies. Moreover, the follow-up period may not be sufficient to identify the beneficial effects of the implant on the patient's craniomaxillofacial growth, development, and aesthetic appearance. If the present study demonstrates that the implant is feasible and safe for the patient, future advanced clinical trials should be conducted using longer follow-up periods to allow the patient's cranio-maxillofacial structures to grow and develop.

ETHICS AND DISSEMINATION

This study was approved by the Committee of Ethics in Research with Medicinal Products (CEIm), reference FIB-BIO-2023-03 (date of approval, November 21, 2023). As an advanced therapy study, the BIOCLEFT clinical trial was authorized by the Spanish Medicines Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS*), reference 2023-506913-23-00/ID:10008 (date of approval, November 21st, 2023). AEMPS will audit the development of the trial. The study was performed in compliance with the Declaration of Helsinki and the principles of Good Clinical Practice. All legal guardians signed an informed consent form before study entry (Supplementary Material S4). This clinical trial was registered at ClinicalTrials.gov (registration number NCT06408337). The results of the clinical trials will be published in a peer-reviewed journal.

AUTHOR CONTRIBUTIONS

AEL, RFV, EC, BQ, EA, GC, and MA conceived and designed the study. The clinical trial was conducted by all the authors, with AEL, RFV, AMP, DV, and ELL participating in the surgical procedures; IG, MAMP, VC, FC, JCA, ODGG, DSP, PAF, MEE, AC, and MA participated in the design and quality control of the medicinal product evaluated in the present work; and AEL, RFV, EC, BQ, EA, GC, and MA participated in the generation of the documents and protocols required for the clinical trial. AEL, RFV, and MA wrote the first version of the manuscript. IG, MAMP, VC and AC revised the manuscript and provided valuable information. M.A. is responsible for the overall content as guarantor. All the authors have read and approved the final version of the manuscript.

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COMPETING INTERESTS

None declared.

DATA STATEMENT

This study was registered at ClinicalTrials.gov (NCT06408337) and EuclinicalTrials. gov (2023-506913-23-00). Results are not available yet.

PATIENT AND PUBLIC INVOLVEMENT

The patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this study.

PATIENT CONSENT FOR PUBLICATION

Not applicable.

FIGURE LEGENDS

Figure 1. Design of the BIOCLEFT clinical trial. The different phases and groups of patients are represented at each stage of the trial.

Figure 2. Stages of the BIOCLEFT clinical trial and investigations that will be conducted at each visit. The approximate moment when each visit will be programmed is shown to the left of the visit number, and the relevant analyses are represented with symbols (explained below the figure). PS: postsurgery. *Visit 2 will take place approximately 30 days before the surgical procedure.

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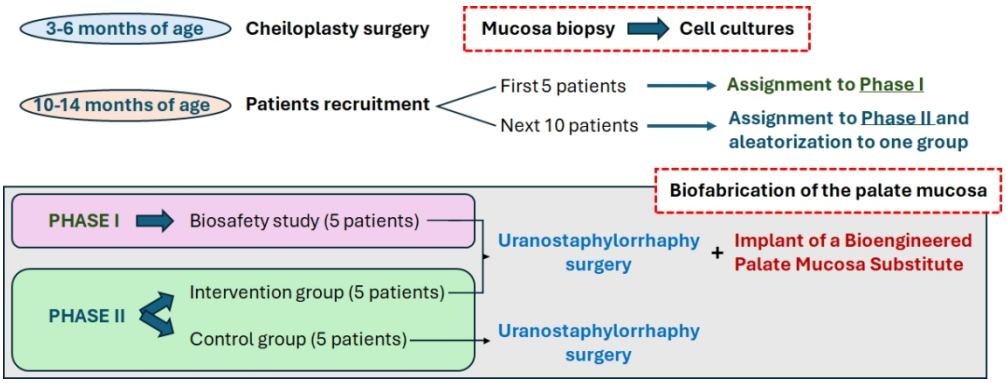

Figure 1

103x38mm (300 x 300 DPI)

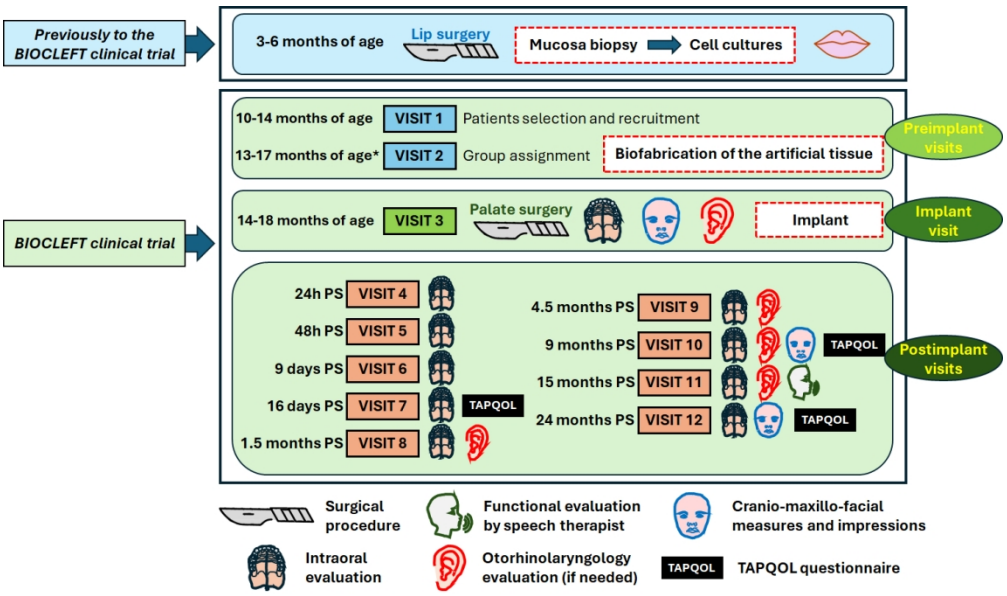

Figure 2

127x75mm (300 x 300 DPI)

Supplementary Table S1. Questionnaire used to assess feasibility of the procedure.

SURGEON SATISFACTION QUESTIONNAIRE. Each question must be rated using a Likert-like scale ranging from 1 to 5	VERY BAD (1)	BAD (2)	AVERAGE (3)	GOOD (4)	EXCELLENT (5)
1. GENERAL APPEARANCE AND ASPECT OF THE BIOCLEFT AUTOLOGOUS PALATE MUCOSA GENERATED BY TISSUE ENGINEERING USING NANOSTRUCTURED FIBRIN-AGAROSE BIOMATERIALS GRAFTED IN CHILDREN WITH CLEFT LIP AND PALATE					
1.1. The product has an adequate aspect, is homogeneous and is devoid of any apparent defects?					
1.2. The size of the product is adequate for use in patients affected by cleft lip and palate?					
1.3. The color of the product is compatible with a normal tissue?					
1.4. Is it easy to identify both tissue layers of the product (epithelium and connective tissue)?					
2. HANDLING THE BIOCLEFT PRODUCT					
2.1. Can this product be easily extracted from the recipient in which the tissue substitute has been delivered to the operating room?					
2.2. Can this product be easily handled using surgical forceps?					
2.3. Can this product be easily trimmed and adapted to the surgical site using a scalpel or other surgical instrument?					
2.4. Can this product be easily placed at the palate defect area?					
2.5. Can this product be easily sutured at the palate defect area?					
2.6. Has this product the capabiity to adhere to the palate defect area?					
3. RESULTS OF THE IMPLANT					
3.1. Has this product efficiently covered the palate defect area?					
3.2. Once grafted, is the aspect of the implant adequate?					
3.3. Once grafted, has the implant a homogeneous aspect, without bubbles and without any detectable defects?					
3.4. Overall, do you think the implant of the product has been feasible?					
3.5. In general, do you think the implant of the BIOCLEFT product has been easy?					

Supplementary Table S2. Questionnaire used to assess the patient's aesthetic appearance.

PATIENT AESTHETIC EVALUATION. Each question must be rated using a Likert-like scale ranging from 0 to 4	NO IMPROVEMENT (0)	25% IMPROVEMENT (1)	50% IMPROVEMENT (2)	75% IMPROVEMENT (3)	100% IMPROVEMENT (4)
1. LIP EVALUATION					
1.1. Lip symmetry					
1.2. Shape of the philtrum					
1.3. Visibility of the scar					
1.4. Symmetry of the dry/wet line					
1.5. Lip fullness					
2. NOSE EVALUATION					
2.1. Symmetry of the nose tip					
2.2. Symmetry of the nostrils					

FIBAO Fundación para la Investigación Biosanitaria de Andalucía Oriental. Alejandro Otero.

DATA MANAGEMENT PLAN (DMP)

Clinical trial title: Phase I-IIa, Randomized, Controlled, Open-label, Single-center Clinical Trial to Evaluate Safety, Feasibility, and Efficacy of the Use of BIOCLEFT in the Treatment of Patients with Cleft Palate (BIOCLEFT clinical trial)

Protocol number: FIB-BIO-2023-03

Sponsor: Fundación para la investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO)

Creator: Miguel Alaminos

Principal Investigators: Miguel Alaminos and Ricardo Fernández-Valadés

Affiliation: University of Granada and University Hospital Virgen de las Nieves, Granada, Spain

Template: DCC Template

ORCID iD: 0000-0003-4876-2672 (MA) and 0000-0001-8087-4311 (RFV)

Project abstract:

Introduction. Current gold-standard treatment for patients with orofacial cleft is the surgical repair of the palatal defect (uranostaphylorrhaphy), which is associated to growth defects and hypoplasia of the maxillofacial structures. This study will analyze the potential of a bioengineered model of artificial palate mucosa generated by tissue engineering using autologous stromal and epithelial cells and nanostructured fibrin-agarose biomaterials to improve the results of the treatment of patients with unilateral cleft palate and lip.

Methods and analysis. A phase I-IIa clinical trial was implemented to determine the feasibility and biosafety of a procedure in which a bioartificial palate mucosa is grafted on the areas of denudated bone in patients subjected to uranostaphylorrhaphy. Control patients will receive the standard surgical treatment. 5 patients will be included in the first biosafety phase of the study. A second phase will be implemented with 10 patients randomly assigned to the intervention or control groups (1:1). The intervention group will receive standard surgical treatment followed by application of an autologous bioartificial palate mucosa. Feasibility will be analyzed at the moment of surgery. 9 postimplant visits are scheduled in a 2-year follow-up period, in which local and systemic biosafety will be analyzed by determining the evolution of the graft (signs of necrosis, rejection, inflammation, etc.) and the patient. Preliminary signs of efficiency will be also explored by sequentially evaluating cranio-maxillo-facial development, hearing impairment, speech capability and the quality of life of the family. When available, results will be published in journals and posted in relevant repositories.

Ethics and dissemination. The study was approved by the Committee of Ethics in Research with Medicinal Products (CEIm) and authorized by the Spanish Medicines Agency (AEMPS). Results of the study will be published in peer-reviewed journals.

Trial registration. ClinicalTrials.gov: NCT06408337; Euclinicaltrials.eu: 2023-506913-23-00.

ID: 162342

Start date: 17-04-2024

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BIOCLEFT CLINICAL TRIAL

DATA COLLECTION

The data to be collected are described in the study protocol, and include:

- Participant information: ID, demographics, previous medical history.
- Inclusion/exclusion criteria.
- Treatment details.
- Outcome Measures (primary and secondary outcome data):
  - Feasibility data of the implant procedure.
  - Biosafety data of the implant procedure.
  - Effects of the implant on patient's growth, development and life quality.
  - Adverse events

The data collection process will be performed in a validated electronic Case Report Form (eCRF), by capturing data from participants enrolled in the study. Each participant's demographics, medical history, treatment details, and outcome measures will be entered in real time by trained site staff using an intuitive eCRF interface. Automated validation checks immediately flag any discrepancies, ensuring data accuracy from the outset. Regular source data verification will be conducted by the CRA to confirm that the data recorded aligns with the original documentation, maintaining compliance with regulatory standards.

DOCUMENTATION AND METADATA

As an advanced therapies clinical trial, the data will be accompanied by all the protocols and documents associated to this trial. The trial was approved by the Spanish Medicines Agency.

ETHICS AND LEGAL COMPLIANCE

As a clinical trial approved by the Spanish Medicines Agency, all legal issues are covered. The project has been approved by several ethics and research committees, including:

- Committee of Ethics in Research with Medicinal Products (CEIm) in Seville, reference FIB-BIO-2023-03 (date of approval, November 21th, 2023).
- Authorized by the Spanish Medicines Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS*), reference 2023-506913-23-00/ID:10008 (date of approval, November 21st, 2023).

STORAGE AND BACKUP

As an advanced therapies clinical trial, the sponsor and the PIs will securely custody the data for at least twenty-five years following the completion of the trial.

Data will be preserved in digital form and custodied at the University Hospital Virgen de las Nieves, following all the security measures established for this type of studies, controlled by the clinical trial monitorization committee.

The PIs and the monitor are the only persons authorized to access the data. Other researchers could request partial access to the data.

DATA SHARING STATEMENT

Individual deidentified participant data will be shared, including data dictionaries, to promote transparency and further research in the field. The data shared will include demographic information, clinical outcomes and any adverse events reported during the trial. In addition to participant data, the following documents will be available: protocol and informed consent.

The results of the clinical trial will be made publicly available in the Clinical Trials Information System (CTIS) and on ClinicalTrials.gov. Since the trial is being conducted in Spain, it will adhere to the European regulations for the publication of results, which require that results be published within 12 months of trial completion. Additionally, the main

results and conclusions will be published in open-access journals and spread in scientific meetings and congresses to further disseminate our findings to the scientific community.

Non-personal data and data that are not considered to have ethical concerns or sensitive character will be deposited, whenever possible, in public repositories such as Zenodo or Digibug. Restrictions will affect the personal data and other data that could be sensitive or have ethical concerns.

RESPONSIBILITIES AND RESOURCES

Data management will be performed by the PIs of the project and the professionals in the Andalusian Network for the design and translation of Advanced Therapies participating in the clinical trial.

The data will be delivered using public repositories such as Zenodo or Digibug.

Junta de Andalucía

Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

HOJA DE INFORMACIÓN PARA LA PARTICIPACIÓN DEL SUJETO EN EL ENSAYO CLÍNICO Y CONSENTIMIENTO INFORMADO POR REPRESENTACIÓN

Título: Ensayo clínico fase I-IIa, aleatorizado, controlado, no enmascarado y unicéntrico, para evaluar la seguridad, factibilidad e indicios de eficacia del uso de un sustituto autólogo de mucosa palatina humana de fibrina-agarosa nanoestructurada generado por ingeniería tisular, en el tratamiento de pacientes con fisura palatina.

Código protocolo: FIB-BIO-2023-03

Eu CT number: 2023-506913-23-00

Promotor: Fundación para la Investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO)

Investigador Principal: Ricardo Fernández Valadés

Centro: Hospital Universitario Virgen de las Nieves

INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un ensayo clínico, que es un estudio de investigación para poder encontrar mejores tratamientos para niños con Fisura Labio Palatina, como la que presenta su hijo, en el que le invitamos a participar.

El estudio ha sido **aprobado** por el Comité de Ética de la Investigación con medicamentos de Sevilla, que pertenece a la Red de Comités de Ética del Sistema Sanitario Público de Andalucía, y por la Agencia Española de Medicamentos y Productos Sanitarios, de conformidad con la legislación vigente en materia de ensayos clínicos con medicamentos, el Reglamento Europeo 536/2014, de 16 de abril y el Real Decreto 1090/2015, de 4 de diciembre.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir **si quiere o no que su hijo/a participe** en este ensayo. Para ello, lea esta hoja de información con atención y pregunte a su médico las dudas que le puedan surgir. Se le entrega, además, una copia de este documento para que pueda valorarlo y consultarlo con las personas que considere oportuno.

PARTICIPACIÓN VOLUNTARIA

Le invitamos a participar en el estudio porque su hijo/a presenta una lesión en el paladar consistente en una fisura unilateral total.

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La **participación de su hijo/a es voluntaria**, por lo que puede decidir no participar. Si decide otorgar su consentimiento y que su hijo/a participe en el estudio, podrá cambiar su decisión en cualquier momento, sin que por ello se altere la relación con su médico, ni se produzca perjuicio alguno en su atención sanitaria.

¿EN QUÉ CONSISTE EL ENSAYO CLÍNICO?

Las fisuras del labio y del paladar son orificios o hendiduras del labio superior, del techo del paladar, o de ambos. Se producen cuando estas estructuras de la cara no se cierran por completo durante el embarazo. La fisura labio-palatina conlleva alteraciones funcionales y estéticas de varias estructuras que, según los casos, producen alteraciones de la pronunciación de las palabras, al tragar, deformidad de labios, nariz y paladar, de la musculatura de la faringe y de la posición de los dientes, así como posibles alteraciones en la salida de los dientes temporales o definitivos, y del crecimiento de los huesos de la cara.

Para cerrar estas fisuras se realizan intervenciones que son bastante complejas, y que están destinadas a mejorar el aspecto estético y la función, y según los casos la mejora de la alimentación, evitar la salida de comida por la nariz, mejora de la pronunciación, y el correcto alineamiento de ambas arcadas dentarias. La complejidad puede hacer que el aspecto exterior de la zona operada no sea totalmente normal.

Este paladar artificial, que llamamos BIOCLEFT, es un medicamento de terapia avanzada. Está elaborada a partir de células donadas por su propio hijo/a, en cultivo y materiales naturales: fibrina (proteína obtenida de sangre), y agarosa (producto natural extraído de algas). Mediante el procesamiento de la muestra donada previamente, se obtendrán en el laboratorio cultivos celulares de los dos tipos de células que conforman el paladar. Una vez multiplicadas estas células en el laboratorio serán introducidas en una matriz de fibrina y agarosa para fabricar el paladar artificial humano.

OBJETIVO DEL ESTUDIO

El **objetivo** del presente estudio es confirmar que es posible y seguro utilizar un sustituto de mucosa oral, BIOCLEFT, fabricado a partir de una muestra de la propia mucosa de su hijo/a, y si este uso mejora los resultados estéticos y funcionales del tratamiento quirúrgico habitual, en relación con el cierre de las zonas fisuradas, y una reconstrucción más correcta, en los niños/as que, como su hijo/a, presentan una fisura del labio y del paladar.

DESCRIPCIÓN DEL ESTUDIO

Se trata de un ensayo clínico que se realizará en un único hospital.

Los pacientes serán seleccionados de entre los que acudan a la Unidad de Cuidados de labio Leporino y paladar hendido y malformaciones craneofaciales (CLPU) del Hospital Universitario Virgen de las Nieves de Granada. y se incluirán en el mismo, siempre que cumplan todos los criterios de inclusión y ninguno de exclusión.

En este estudio participaran 15 niños, afectados de fisura labial y palatina completa unilateral. Todos ellos serán sometidos a la cirugía de reconstrucción habitual.

De los 15 niños, en 10 de ellos, en la misma intervención de la cirugía de reconstrucción habitual, la zona operada se recubrirá con el medicamento que se está estudiando (grupo experimental) y los otros 5 recibirán solamente la cirugía de reconstrucción habitual.

El estudio se realizará en 2 etapas: los 5 primeros niños que se incluyan, recibirán todos ellos el tratamiento en estudio. En una segunda etapa, los 10 niños restantes, tendrá una probabilidad del 50% de recibir el tratamiento en investigación y una probabilidad del 50% de recibir el tratamiento estándar. El que a su hijo/a le corresponda el grupo experimental o el grupo control, dependerá del azar. Usted sabrá en qué grupo le ha tocado participar.

Ambos procedimientos quirúrgicos se realizarán bajo anestesia general.

Los niños de ambos grupos recibirán la misma terapia de reconstrucción habitual y serán sometidos a un mismo protocolo de cuidado de la herida, seguimiento y evaluación.

En el ensayo se ha establecido un Comité Independiente de Seguridad y Monitorización de Datos para analizar los resultados que se vayan produciendo, y este Comité, una vez tratados los 5 primeros niños, según los datos obtenidos, decidirá si se continua o no con la inclusión de los 10 pacientes restantes.

Se facilitarán al promotor los resultados de todos sus análisis de sangre, así como otros resultados analíticos. Estos resultados están codificados de manera que el promotor no sabe a quién pertenecen dichos resultados. Los resultados positivos del VIH y de la hepatitis viral se comunicarán a las autoridades sanitarias locales tal como marca la legislación sanitaria.

¿CUÁNTO DURARÁ MI PARTICIPACIÓN EN EL ESTUDIO?

Una vez que usted acepte que su hijo/a participe en el estudio, su participación durará aproximadamente 2 años. Durante este periodo deberá acudir a 12 visitas: dos visitas antes de la intervención quirúrgica estándar e implante de BIOCLEFT, si le corresponde, una visita para el implante y 9 visitas de seguimiento tras la intervención.

Los procedimientos a seguir en cada visita, así como el número de visitas serán los mismos para todos los pacientes. El calendario de las visitas se recoge en el ANEXO 1 a este documento.

Además, de las visitas descritas en el protocolo, se podrán realizar todas las visitas intermedias que el médico responsable considere oportuno.

RIESGOS Y MOLESTIAS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Su participación en el estudio podría ocasionar un conjunto de riesgos e incomodidades que se pueden derivar de:

La participación en el Ensayo Clínico, ya que usted y su hijo/a deberán atender a todas las visitas recogidas en el protocolo y en el ANEXO 1, hasta completar el seguimiento.

Además, será necesario realizar una serie de evaluaciones clínicas y se le pedirá que complete algunos cuestionarios. Además, en algunas de ellas se tomarán fotografías de la cara y moldes de la arcada dentaria de su hijo/a, para ir comprobando la evolución. Por último, la extracción de sangre que se realizará al inicio del estudio conlleva un riesgo mínimo, pudiendo producir molestias como dolor y hematoma leve (acúmulo de sangre en la piel) en la zona de punción.

Para valorar la apariencia estética y los cambios que se vayan produciendo en respuesta al tratamiento, se le realizarán a su hijo/a, fotografías de la cabeza (cara y cráneo), en diferentes visitas (Visita 1, 3, 10 y 12). Estas fotografías serán estudiadas por un cirujano experto, y podrán ser empleadas posteriormente en publicaciones científicas. En la fotografía se ocultará la zona de los ojos con mancha negra para evitar el reconocimiento facial del paciente.

Los riesgos derivados de la cirugía son comunes al grupo control y al grupo experimental. A pesar de la correcta técnica quirúrgica pueden presentarse efectos indeseables derivados de la intervención:

- Los riesgos frecuentes y no graves dependen del grado de alteración presente en el labio, y del estado del paciente, son: Hemorragia o infección de la herida quirúrgica, problemas de cicatrización, separación de los bordes de la herida o

aparición de fístulas entre la boca y la nariz, asimetría de la nariz y del contorno del labio, dificultad para la pronunciación de algunos sonidos y por último imposibilidad de cierre completo.

- Los riesgos más graves e infrecuentes que pueden darse son: Necrosis de alguna de las zonas de la piel que se utiliza para cerrar la fisura del paladar, del labio o de la nariz; pueden ocurrir, pero son muy infrecuentes las complicaciones derivadas del uso de material de quirófano (bisturí eléctrico, manta térmica, etc.) o las complicaciones posturales.

- Otros riesgos son los relacionados con la anestesia empleada: El riesgo anestésico depende de muchos factores como son el tipo y la gravedad de la patología que motiva la operación, si se realiza de urgencia, otras enfermedades que padezca el/la paciente, o su edad, puede aumentar los efectos secundarios. Los más frecuentes son: náuseas y vómitos, afecciones en la garganta en caso de intubación; vértigos y trastornos de la visión, temblores, dolor de cabeza, picores, dolores musculares, articulares y dolor de espalda. En las horas que siguen a la anestesia pueden aparecer trastornos pasajeros de memoria, de la atención o del comportamiento del niño. Los más graves son: paso del contenido del estómago a los pulmones, aunque es muy raro si se ha respetado el ayuno preoperatorio, complicaciones imprevisibles que puedan poner en peligro la vida de su hijo como una reacción alérgica verdadera, una hipertermia (fiebre) maligna, insuficiencia respiratoria o una parada cardiaca. La muerte en el curso de una anestesia es muy rara y casi siempre es la consecuencia de un conjunto de complicaciones simultáneas.

Riesgos derivados de medicamento en investigación:

Hasta el momento no se han descrito efectos tóxicos por la administración de los elementos usados para la fabricación de la mucosa artificial, como son la fibrina, la agarosa y las células de la mucosa oral. Esto no significa que no pudiera producirse alguno. Al tratarse de un tratamiento en investigación, éste es uno de los aspectos a valorar desde el punto de vista de seguridad.

El medicamento puede contener trazas derivadas del proceso de fabricación de Gentamicina y de Anfotericina B. Si usted conoce que su hijo presente alergia a estos medicamentos, debe ponerlo en conocimiento del personal facultativo encargado de la intervención.

Se harán todas las pruebas y tratamientos necesarios para que los riesgos de la intervención y de las pruebas de evaluación se reduzcan al mínimo.

¿CUÁLES SON LOS BENEFICIOS ESPERADOS?

Basándonos en la evidencia científica, se espera que el tratamiento propuesto mejore el cierre de las zonas fisuradas y como consecuencia que su hijo/a presente un aspecto parecido al de cualquier otro niño que no haya nacido con la lesión, así como la mejora de ciertas funciones como son el habla, la deglución, audición, etc.

En cualquier caso, con su participación en el estudio contribuirá a mejorar el conocimiento sobre posibles alternativas para tratar su enfermedad, colaborando de este modo en el avance científico de la sociedad.

¿CUÁL ES MI COMPROMISO?

Usted se compromete a **acudir junto con su hijo/a a las visitas y a que se someta a las pruebas programadas,** notificar cualquier **evento adverso** que le suceda a su hijo/a, tenga o no relación con el ensayo clínico y a comunicar los **cambios realizados en su medicación,** si los hay. En caso de que deje de acudir a las visitas de seguimiento sin haber revocado expresamente su consentimiento, el promotor podrá completar su seguimiento clínico mediante el acceso a su historial médico en el centro y recogida de datos para el estudio.

Asimismo, deberá **comunicar a los distintos profesionales de la salud** con los que tenga relación que su hijo/a está participando en este ensayo clínico, advirtiéndoles que, por motivos de seguridad y posibles contraindicaciones con el medicamento en investigación, no deben modificar la medicación que esté tomando sin consultar antes con el médico del estudio en el caso de que tenga medicación prescrita.

SI TENGO ALGUNA DUDA O CONSULTA, ¿A QUIÉN ME DIRIJO?

Puede **realizar todas las preguntas que desee** y saber más sobre este ensayo clínico, **ahora o en cualquier momento** en el curso del mismo. Además, si observa que su hijo/a experimenta cualquier **evento adverso**, debe contactar inmediatamente con el médico del estudio.

Investigador del estudio: D. Ricardo Fernández Valadés.

Teléfono: ……

Email: ……

Hospital: Hospital Universitario Virgen de las Nieves

En caso de necesitar atención médica de urgencia puede dirigirse al centro habitual de su hijo/a, deberá **comunicar a los distintos profesionales de la salud** con los que tenga relación que está participando en este ensayo clínico y facilitar toda la información posible relativa al estudio.

¿QUÉ TRATAMIENTOS ALTERNATIVOS EXISTEN?

Es importante que sepa que en caso de no querer que su hijo/a participe en el ensayo clínico que se le propone, el investigador responsable del desarrollo del ensayo clínico le indicará las alternativas paliativas o curativas actualmente disponibles para el manejo de su enfermedad.

No dude en consultar con el investigador responsable del desarrollo del ensayo clínico cualquier duda que tenga o si necesita cualquier aclaración sobre esta cuestión.

GASTOS Y COMPENSACIÓN ECONÓMICA

El Promotor del estudio gestiona los aspectos económicos del mismo. Para la realización del estudio la Fundación Pública Andaluza para la Investigación Biosanitaria en Andalucía Oriental- Alejandro Otero ha firmado el correspondiente contrato para su realización. Se trata de un ensayo clínico realizado dentro del sistema público. Ni el centro ni el equipo investigador recibirán compensación económica alguna. Su participación en el estudio no le supondrá ningún gasto adicional a la práctica clínica habitual de su enfermedad.

¿QUÉ TRATAMIENTO RECIBIRÉ CUANDO FINALICE MI PARTICIPACIÓN EN EL ESTUDIO?

Una vez finalice su participación en el estudio, su hijo/a recibirá el tratamiento que su médico considere más adecuado para su situación clínica.

PÓLIZA DE SEGURO

El Promotor del estudio dispone de una póliza de seguros que se ajusta a la legislación vigente (Real Decreto 1090/2015), que le proporcionará la compensación e indemnización en caso de menoscabo de la salud de su hjo/a o de lesiones que pudieran producirse en relación con su participación en el estudio, siempre que no sean consecuencia de la propia enfermedad que se estudia o de la evolución propia de la misma como consecuencia de la ineficacia del tratamiento. Dicha póliza, ha sido contrata con la compañía aseguradora **HDI Global**. Si desea más información relativa a este apartado, consulte con el investigador principal del estudio en su centro.

¿QUIÉN TIENE ACCESO A MIS DATOS?

Tanto el promotor como el centro se asegurarán de que se cumplan los principios contemplados en la normativa de protección de datos, tanto nacional como europea

Para obtener más información sobre la confidencialidad y la protección de datos de carácter personal, consulte el Apéndice 1.

¿PARA QUÉ SE UTILIZAN MIS DATOS?

Sus datos son necesarios para que el promotor desarrolle el medicamento, obtenga permiso para introducirlo y mantenerlo en el mercado, supervise su seguridad y lo cubra el seguro de salud, es decir, durante todo el programa de desarrollo de medicamentos. Por lo tanto, se utilizarán según lo planeado en este estudio, así como dentro de las actividades de investigación relacionadas necesarias para este programa de desarrollo de medicamentos con el fin de:

- comprender cómo funcionan el medicamento del estudio y medicamentos similares en el organismo (es decir, evaluar el modo de acción del medicamento del estudio),
- comprender mejor la enfermedad estudiada y los problemas de salud asociados,
- desarrollar pruebas de diagnóstico para la enfermedad,
- aprender del presente estudio para planificar nuevos estudios o mejorar los métodos de análisis científico,
- publicar los resultados de la investigación en revistas científicas o utilizarlos con fines educativos.

OTRA INFORMACIÓN RELEVANTE

Una descripción de este ensayo clínico estará disponible en **http://reec.aemps.es** según exige la legislación española. Encontrará igualmente información sobre el estudio en **https:// https://clinicaltrials.gov**. Además, transcurrido un año desde la finalización del estudio, estarán disponibles en la base de datos de la Unión Europea el resumen de sus resultados (independientemente de cuáles sean), así como un resumen redactado en un lenguaje comprensible para una persona.

Cualquier nueva información referente a las terapias utilizadas en el estudio y que pueda afectar a su disposición para que su hijo/a participe en el estudio, que se descubra durante su participación, le será comunicada por su médico lo antes posible.

Si la nueva información implica alguna modificación de la hoja de información, se le facilitará la nueva versión del documento, dándosele la oportunidad de decidir si desea que su hijo/a continúe su participación en el estudio.

¿CUÁNDO FINALIZA MI PARTICIPACIÓN EL ENSAYO?

El investigador, el Promotor, el Comité de ética y las autoridades reguladoras que supervisan este ensayo clínico pueden decidir retirar a su hijo/a si consideran que es lo mejor para él/ella.

- Una vez **concluido el periodo de seguimiento** que tendrá una duración de aproximadamente 24 meses, desde la firma del consentimiento.
- **En cualquier momento si usted lo decide**, debiendo comunicarlo al investigador.
- Si el **médico del estudio decidiera suspender la participación de su hijo/a** en el ensayo, por haberse aprobado un nuevo medicamento con mayor eficacia demostrada, por considerar que es lo mejor para su hijo/a, o si usted no siguiese los procedimientos del ensayo clínico, usted recibirá una explicación adecuada del motivo que ha ocasionado la retirada de su hijo/a del estudio.
- Por otras **circunstancias imprevistas,** siempre que el Promotor o las Autoridades Sanitarias lo consideren oportuno.

En todo caso, deberá seguir las indicaciones que le transmita el médico del estudio, para una finalización ordenada del ensayo.

¿QUÉ OCURRIRÁ CON MIS MUESTRAS?

Las muestras de sangre recogidas se asociarán a un código que solo podrá ser relacionado con la identidad de su hijo/a y con su historia clínica por el médico del estudio/colaboradores. Los datos que se deriven de la utilización de estas muestras se tratarán del mismo modo que el resto de datos que se obtengan durante el ensayo. Sus muestras y los datos asociados podrán ser analizados en diversos laboratorios, para los mismos fines del estudio descrito, pero siempre manteniendo la confidencialidad de su identidad de acuerdo a la legislación vigente.

AGRADECIMIENTO:

Sea cual sea su decisión, el promotor y el equipo de investigación quieren agradecer su tiempo y atención.

Junta de Andalucía

Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

Junta de Andalucía

Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

HOJA DE CONSENTIMIENTO DE PARTICIPANTE ANTE TESTIGOS Y/O FAMILIAR/PERSONA VINCULADA DE HECHO

Título: Ensayo clínico Fase I-IIa, unicéntrico, controlado, abierto y aleatorizado, para evaluar la seguridad, factibilidad e indicios de eficacia del uso de un sustituto autólogo de mucosa palatina humana de fibrina-agarosa nanoestructurada generado por ingeniería tisular, en el tratamiento de pacientes con fisura palatina.

Código de protocolo: FIB-BIO-2023-03

Eu CT number: 2023-506913-23-00

Yo,_____

_____<<*nombre y apellidos* ***del padre o tutor legal*** >> como

☐ Padre/madre / ☐ Tutor legal, afirmo que he recibido una explicación satisfactoria sobre el procedimiento del estudio, su finalidad, riesgos, beneficios y alternativas por parte del D/Dª

_____

<<*nombre y apellidos del investigador*>> y que he leído la hoja de información que se me ha entregado sobre el estudio, de modo que:

☐ Ha podido hacer preguntas sobre el estudio

☐ Ha recibido suficiente información sobre el estudio.

☐ Ha hablado con

_____

<<*nombre del investigador*>>

☐ Comprende que su participación es voluntaria.

☐ Comprende que puede retirarse del estudio:

- Cuando quiera,
- Sin tener que dar explicaciones y
- Sin que esto repercuta en los cuidados médicos de mi hijo/a.

El participante acepta que se tomen muestras de su hijo/a para los mismos fines del estudio descrito:

☐SÍ ☐ NO

El padre, madre o tutor legal del participante desea que le comuniquen la información derivada de la investigación que pueda ser relevante para su salud:

☐SÍ ☐ NO

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Presto libremente mi conformidad para que mi hijo/a participe en el estudio.

Firma del representante legal, primer progenitor o persona vinculada de hecho: Fecha: Nombre, firma y fecha de puño y letra por el firmante	Firma del investigador y Nº de colegiado Fecha:

Firma del segundo progenitor (o tutor legal) del menor: <<Nombre y fecha de puño y letra del firmante>>	Fecha: <<fecha de puño y letra del firmante>>

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Apéndice 1. Protección de datos de carácter personal relativo al documento Hoja de información al paciente y CI del estudio

Título del estudio	Ensayo clínico Fase I-IIa, unicéntrico, controlado, no enmascarado y aleatorizado, para evaluar la seguridad, factibilidad e indicios de eficacia del uso de un sustituto autólogo de mucosa palatina humana de fibrina-agarosa nanoestructurada generado por ingeniería tisular, en tratamiento de pacientes con fisura palatina.
Código del estudio	FIB-BIO-2023-03
EU CT Number	2023-506913-23-00
Promotor	Fundación para la Investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO)
Investigador Principal	Ricardo Fernández valades
Centro	Hospital Universitario Virgen de las Nieves

De conformidad con lo establecido en el Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos y en la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales, es importante que conozca la siguiente información:

La Fundación para la Investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO) es el promotor de este estudio. Tiene su sede en Granada. Tanto el Centro como el Promotor son responsables de sus respectivos tratamientos, correspondiendo a cada uno de ellos las obligaciones derivadas de su actividad. El centro es el responsable de todos los datos que figuren en la historia y que puedan identificarle y el promotor de los que se recogen en este estudio de forma codificada; es decir, durante su participación en el estudio se le identificará mediante un código y ni el investigador, ni el hospital transferirán al promotor información alguna que pueda identificarle directamente.

La lista que relaciona el código de identificación con los datos que le identifican (nombre, apellido, número de historia clínica…) se guardan de manera confidencial en su centro sanitario.

¿QUÉ OCURRE CON LA CONFIDENCIALIDAD?

El acceso a su información personal identificada quedará restringido al médico del estudio y colaboradores, autoridades sanitarias (Agencia Española de Medicamentos y Productos Sanitarios, autoridades sanitarias extranjeras), al Comité de Ética de la Investigación con medicamentos (CEIm) y personal autorizado por el promotor (monitores del estudio o auditores), cuando lo precisen para comprobar los datos, procedimientos del estudio, y el cumplimiento de normas de buena práctica clínica; pero siempre manteniendo la confidencialidad de los mismos. La identidad de su hijo/a podría ser revelada en casos excepcionales, como situaciones de urgencia médica para su salud o requerimiento legal. El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustarán a lo dispuesto en la normativa aplicable.

Igualmente, en caso de producirse una reacción adversa, los datos identificativos podrán ser comunicados por el Centro a las autoridades sanitarias competentes y a las compañías aseguradoras con las que se hubiese contratado un seguro, a fin de llevar a cabo las gestiones que resulten necesarias.

Los datos codificados pueden ser transmitidos a terceros y a otros países, pero en ningún caso contendrán información que pueda identificar directamente a su hijo/a, como nombre y apellidos, iniciales, dirección, nº de la seguridad social, etc. En el caso de que se produzca esta cesión, será para los mismos fines del estudio descrito o para su uso en publicaciones científicas, pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación vigente.

¿DURANTE CUÁNTO TIEMPO SE GUARDARÁN MIS DATOS?

El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de la salud de su hijo/a.

¿QUÉ DERECHOS TENGO?

Con respecto a los datos, su hijo/a tiene los siguientes derechos que usted podrá ejercer ante el investigador principal y/o centro:

- Puede preguntar en cualquier momento qué datos se están guardando (derecho de acceso), quién los usa y con qué fin; puede solicitar una copia de los datos personales para su propio uso.

- Puede solicitar recibir una copia de los datos personales proporcionados por usted para transmitirlos a otras personas (portabilidad).
- Puede corregir los datos personales de su hijo/a proporcionados por usted y limitar el uso de datos que sean incorrectos (derecho de rectificación y supresión).
- Puede oponerse al uso de los datos personales o restringirlo (derecho de oposición)

Le recordamos que existen algunas limitaciones con objeto de garantizar la validez de la investigación y cumplir con los deberes legales del promotor y los requisitos de autorización de medicamentos. Si decide que su hijo/a deje de participar en el ensayo o retirar su consentimiento sobre el tratamiento de los datos no se podrán eliminar aquellos datos recogidos hasta ese momento. Debe saber que si decide retirar el consentimiento sobre el tratamiento de los datos podría determinar su cese en la participación en el ensayo.

¿CON QUIÉN CONTACTO?

Para ejercitar sus derechos, diríjase al investigador principal del estudio (cuyos datos aparece en la página 8 de la hoja de información superior) o al Delegado/a de Protección de Datos de su Centro, o del promotor.

Delegado de Protección de Datos para todos los centros de la Junta de Andalucía:

Email: dpd.sspa@juntadeandalucia.es

Delegado de Protección de Datos del promotor:

Email: dpd.csalud@juntadeandalucia.es

Así mismo, tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho (a través de su página web *www.aepd.es*).

¿CÓMO SE COMUNICARÁN LOS RESULTADOS?

Una descripción de este ensayo clínico estará disponible en https://reec.aemps.es, según exige la legislación española.

El promotor está obligado a publicar los resultados, tanto positivos como negativos, de los ensayos clínicos autorizados, preferentemente, en revistas científicas antes de ser divulgados al público no sanitario, con independencia de las obligaciones de publicación del informe de los resultados en el Registro Español de estudios clínicos

(REec) y de lo establecido al respecto en el Reglamento (UE) n.º 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014.

Cuando se hagan públicos estudios y trabajos de investigación sobre medicamentos, dirigidos a la comunidad científica, se harán constar los fondos obtenidos por el autor, por o para su realización, y la fuente de financiación.

Se mantendrá en todo momento el anonimato de los sujetos participantes en el ensayo.

SALVAGUARDA PARA LA PROTECCIÓN DE SUS DATOS PERSONALES

Se adoptarán las medidas de protección apropiadas para proteger los datos codificados durante y después del ensayo, entre ellas:

- El acceso a los datos codificados quedará limitado a personas sujetas a obligaciones de confidencialidad (incluida la obligación de no intentar volver a identificar a los pacientes ni descodificar los datos clínicos).
- Los datos codificados se protegerán con medidas de seguridad para evitar su alteración, pérdida y accesos no autorizados y podrán aplicarse medidas adicionales que eviten la identificación.
- Los datos codificados no se compartirán con fines de comercialización directa ni para otros fines que no sean obligaciones legales o que no se consideren investigación científica de conformidad con la legislación vigente en materia de protección de datos. En particular, no se utilizarán para tomar decisiones sobre futuros servicios que se le pudieran ofrecer, como un seguro.

Junta de Andalucía

Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

ANEXO 1. CALENDARIO DE VISITAS Y PROCEDIMIENTOS

Visita	Procedimientos/Evaluaciones
V1 Selección. 4 meses antes de la cirugía.	• Firma del consentimiento informado • Obtención de muestras de sangre, fotografías y Cuestionario de Calidad de Vida.
V2 (Telefónica). 1 mes antes de la cirugía.	• Para confirmar que puede ser incluido en el estudio, y poder asignarle un grupo.
V3 (cirugía)	• Intervención quirúrgica • Revisión por el otorrino, obtención de moldes y fotografías.
V4, 5 y 6 (A las 24, 48 horas, y 7 días de la cirugía	• Revisión de la herida, incluyendo fotografías
V7. A los 14 días de la cirugía	• Revisión de la herida, cuestionario de Calidad de vida y fotografías
V8 y V9. Al mes y medio y 4 meses y medio de la cirugía	• Revisión de la herida y revisión por el otorrino si es necesario.
V10. A los 9 meses de la cirugía	• Revisión, impresiones del paladar y generación de moldes y fotografías. Revisión por el otorrino si es necesario. Cuestionario de Calidad de vida.
V11. A los 15 meses de la cirugía	• Revisión de la herida. Valoración del lenguaje por el logopeda y fotografías
V12. A los 24 meses de la cirugía	• Revisión de la herida. Cuestionario Calidad de vida, fotografías, valoración de la audición por el otorrino si es necesario y del lenguaje por el logopeda.

BMJ Open

A phase I-IIa clinical trial to evaluate the safety, feasibility, and efficacy of the use of a palate mucosa generated by tissue engineering for the treatment of children with cleft palate: the BIOCLEFT study protocol

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Paediatrics
Keywords:	Cleft Palate, Clinical Trial, Cleft Lip, Histology

A phase I-IIa clinical trial to evaluate the safety, feasibility, and efficacy of the use of a palate mucosa generated by tissue engineering for the treatment of children with cleft palate: the BIOCLEFT study protocol

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Euclinicaltrials.eu registration number: 2023-506913-23-00

ABSTRACT

Introduction. The current gold standard treatment for patients with orofacial clefts is surgical repair of the palatal defect (uranostaphylorrhaphy), which is associated with growth defects and hypoplasia of the maxillofacial structures. This trial aims to evaluate the potential of a bioengineered artificial palate mucosa, created through tissue engineering with autologous stromal and epithelial cells and nanostructured fibrin-agarose biomaterials, to enhance treatment outcomes for patients with unilateral cleft lip and palate.

Methods and analysis. This phase I-IIa clinical trial aims to evaluate the feasibility and biosafety of a procedure involving grafting bioartificial palate mucosa onto the areas of denudated bone in patients undergoing uranostaphylorrhaphy. The control patients will undergo standard surgical treatment. Five patients will be included in the first biosafety phase. In the second phase, 10 patients will be randomly assigned to the intervention or control group (1:1). The intervention group will undergo standard surgical treatment followed by the application of autologous bioartificial palate mucosa. Feasibility will be analyzed at the time of surgery. Nine postimplant visits will be scheduled over a 2-year follow-up period, in which local and systemic biosafety will be investigated by determining graft evolution, including signs of necrosis, rejection, inflammation and patient factors. Preliminary signs of efficiency will be explored by sequentially evaluating craniomaxillofacial development, hearing impairment, speech capability, and quality of life of the family. The research will be published in journals and posted in the relevant repositories when available.

Ethics and dissemination. This study has been approved by the Committee of Ethics in Research with Medicinal Products (CEIm) and authorized by the Spanish Medicines Agency (AEMPS). The results of this study will be published in peer-reviewed journals.

Trial registration. ClinicalTrials.gov: NCT06408337; EuclinicalTrials. eu: 2023-506913-23-00.

KEYWORDS

Cleft palate, Cleft lip, Clinical trial, Histology

ARTICLE SUMMARY

Strengths and limitations of this study:

⇒ This study describes the protocol of an advanced therapies clinical trial approved by the Spanish Medicines Agency.

⇒ The clinical trial will assess the feasibility and biosafety of a tissue-engineered, bioartificial palate mucosa for treating children born with orofacial cleft.

⇒ The single-center design could limit the extrapolation of the results.

⇒ The sample size of 15 patients is small, although it could be sufficient for an initial feasibility and biosafety analysis.

INTRODUCTION

Orofacial cleft (OFC) is a congenital defect that affects 1:700 to 1:1000 live births and is the most common congenital defect in developed countries, after only Down syndrome [2]. This condition may affect the patient's lip, palate, or both structures and is usually clinically detected at birth when the different maxillofacial processes are unfused, manifesting as a defect in the lip or hard palate and soft tissues [1]. Orofacial cleft is associated with serious physical, psychological, and social impacts affecting patients and their families [3]. Aside from the primary malformation, patients and their families must also contend with complex surgical interventions and interdisciplinary medical-surgical treatments [4,5]. Typically, management is long and complex and includes surgical corrections, orthodontic treatments, bone grafts, rhinoplasty, psychotherapy, and speech therapy [4]. Moreover, the outcomes of the standard treatments are not always optimal [6].

The gold standard surgical treatment for palatal repair is uranostaphylorrhaphy, which involves obtaining mucosal flaps from the remaining areas of the hard palate and suturing the flaps in the midline to generate a physical barrier between the oral and nasal cavities [7]. Unfortunately, this procedure is associated with impaired maxillofacial growth and hypoplasia of the craniofacial structures. The denudation of the palatal bone disrupts facial growth and development [8,9]. In contrast, other surgical techniques, such as Furlow palatoplasty, which is a buccal myomucosal flap procedure, reportedly offer improved results with fewer impacts on maxillary bone growth in certain patients [10]. In patients with cleft lip and palate, the lip is routinely repaired (cheiloplasty) when the patient is 3–6 months old, whereas the palate is usually repaired surgically approximately one year later when the patient is 15–18 months old [11].

Bioartificial tissues generated by tissue engineering (TE) have been proposed to improve outcomes following surgical repair of OFC. Tissue engineering combines live cells with biocompatible biomaterials and growth factors to generate functional tissue substitutes to replace damaged tissues and organs [12]. In OFC, only a few models of bioartificial tissues generated by TE have been described and evaluated in animal models [13]. One such model is BIOCLEFT, a palatal mucosa substitute generated by our research group using nanostructured fibrin–agarose biomaterials combined with oral mucosal stromal and epithelial cells, including fibroblasts and keratinocytes. Nanostructured fibrin–agarose biomaterials have shown good biocompatibility and promising clinical results in patients with severe corneal ulcers [14] and extensive skin burns [15]. The application of this palate substitute in an animal model of palate damage in newborn rabbits resulted in significant improvement in the development and growth of hard and soft tissues, with a positive outcome in most animals [16]. After a thorough evaluation and characterization of the BIOCLEFT product at the biomechanical, histological, histochemical and immunohistochemical levels [16–18], we obtained approval (date: November, 20th, 2023) from the Spanish Medicines Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS*) to generate BIOCLEFT as an advanced therapy medicinal product (ATMP) and to implement the BIOCLEFT clinical trial in patients affected by cleft palate.

Here, we present the protocol for the phase I-IIa BIOCLEFT clinical trial (protocol version 2, date of approval: October, 19th, 2023. This trial will determine the feasibility and biosafety of this novel TE product in children with cleft palate and will preliminarily evaluate treatment efficacy.

METHODS AND ANALYSIS

Study design

The BIOCLEFT clinical trial will be a phase I-IIa controlled, open-label, randomized, unicentric advanced therapy trial to evaluate the feasibility and safety of an autologous palate mucosa substitute generated by TE in children with cleft palate. The trial coordinator is Dr. Ricardo Fernández-Valadés, and the project principal investigator is Dr. Miguel Alaminos. The sponsor is the Andalusian Network for Design and Translation of Advanced Therapies and FIBAO foundation.

The control group will undergo the gold-standard surgical repair procedure, uranostaphylorrhaphy. In contrast, the study group will be treated with the same procedure, followed by the implantation of a BIOCLEFT substitute used to cover the lateral areas of denudated bone. The professionals involved in the trial will not be blinded to the study.

The uranostaphylorrhaphy procedure used in both groups of patients consists of the closure of the central cleft by suturing the edges of the cleft together. First, the soft tissue (palate mucosa) is carefully detached from the subjacent palate bone on both sides of the palatal defect, taking care not to damage the vascular supply of the soft tissue. The right and left tissues are drawn toward the midline defect and sutured together using silk stitches. This procedure allows a physical barrier to form between the oral and nasal cavities using the palate mucosa; however, the palate bone is left denudated on both sides of the palate grafts. Finally, the uvula, soft palate, and faringopalatine muscles are repaired and sutured to reestablish the normal anatomy of the human pharynx structures.

The first five patients will be sequentially recruited in the initial phase of the clinical trial. As an early phase clinical trial, a safety period of 30 days was established between patients to ensure that the previous patient did not experience any adverse effects due to the implant before subjecting the next patient to the implant. This safety period is a common requirement of national medicine agencies for novel products whose biosafety levels have yet to be determined [19]. The Independent Data Security and Monitoring Committee will perform an interim biosafety analysis after the last patient included in the initial phase reaches 1.5 months of follow-up. This committee consists of 5 members that are independent from the sponsor and are free from any competing interests. If the safety analysis reports that the product is safe, the trial will continue to the second phase. Otherwise, the clinical trial will be terminated.

In the second phase, 10 additional patients with cleft palate will be recruited and randomly assigned to one of the following groups (Figure 1):

1) Control group (n=5), these patients will receive the gold-standard uranostaphylorrhaphy treatment without applying any grafting material.

2) Intervention group (n=5). These children will receive the gold-standard treatment, followed by implantation of the BIOCLEFT artificial palate mucosa, as is the case for patients in the initial phase of the trial. Consequently, this group's total number of patients will be 10 (five in the initial phase and five in the second phase).

This clinical trial was initiated on April 17, 2024. At the time of submission of the present protocol, the clinical trial was in the phase of recruiting five patients for the initial phase of the trial. The study is expected to be completed by December 17, 2028.

Patients and inclusion and exclusion criteria

Children with cleft palate, specifically unilateral cleft lip, will be included in this study. Patients will be recruited at the age of 10–14 months following the cheiloplasty procedure. As described in the Surgical Procedure section, all patients with nonsyndromic cleft palate and unilateral cleft lip will donate a small oral mucosa sample during cheiloplasty. This sample corresponds to the tissue that is usually discarded after cheiloplasty.

Inclusion criteria:

- Pediatric patients, of both genders.
- Diagnosis of total unilateral nonsyndromic cleft lip and palate (FLPNS) that will undergo surgery for correction.
- Children who have previously donated a sample of oral mucosa during the cleft lip repair procedure (cheiloplasty).
- Informed consent signed by one or both parents (or legal guardian) adequately informed of the study and willing to follow the trial procedures and instructions.

Exclusion criteria:

- Active infectious diseases.
- Allergies or hypersensitivity to any of the components or excipients of the investigational product.
- Severe hematological disorders/blood dyscrasias.
- Severe hepatic or renal dysfunction/failure.
- Serious endocrine disorders/dysfunctions.
- Malignant neoplasms.
- Active HIV, HBV, or HCV infection.
- Metabolic bone diseases (Paget's disease, hypercalcemia, etc.).
- Children with cleft lip and palate who present other congenital malformations that, in the researcher's opinion, could affect the outcomes of the trial or the interpretation of results.
- In the opinion of the investigator, any other pathologies that should not be included in the trial for medical or social reasons.

Surgical procedure

All patients enrolled in the study will be treated at the Craniofacial Malformations and Cleft Lip and Palate Management Unit (CMU) of the University Hospital Virgen de las Nieves of Granada, Spain. According to the unit's management protocols, all patients will first undergo cheiloplasty to repair the lip defect. During cheiloplasty, oral mucosal biopsies will be obtained and transferred to a Good Manufacturing Practice (GMP) facility located at the Advanced Therapies Platform of the ibs.GRANADA Research Institute and the University Hospital Virgen de las Nieves of Granada, coordinated by the Andalusian Network for the Design and Translation of Advanced Therapies. From these biopsies, epithelial cells (keratinocytes) and stromal cells (fibroblasts) will be isolated using enzymatic digestion methods, cultured, and expanded as described previously [16,18]. The cell cultures will be cryopreserved for delayed use.

The palatal defect will be repaired in all patients by applying a modified von Langenbeck uranostaphylorrhaphy surgical technique when the patient is approximately 14–18 months old. This procedure involves making two medial and lateral incisions at each side of the palatal cleft, followed by careful detachment of the soft tissue from the palatine bone without damaging its vascular pedicle, to generate a pediculated flap on each side of the palate [20]. Both flaps are then sutured together in the midline of the palate defect to physically separate the oral and nasal cavities. To maintain velopharyngeal function, the muscles are also detached and repaired using sutures [21].

For children in the intervention group, a BIOCLEFT palate mucosa substitute generated by TE will then be surgically applied to cover the denudated areas of the palatine bone on both sides of the hard palate that were exposed during the von Langenbeck surgery. BIOCLEFT will be generated as an ATMP at the Advanced Therapies Platform using autologous stromal and epithelial cells previously cultured from the biopsies taken during cheiloplasty. First, a stromal layer is fabricated using fibrin-agarose biomaterials with cultured fibroblasts. In brief, per mL of volume, 760 µL of human plasma obtained from plasma donors will be combined with 15 µL of tranexamic acid (Amchafibrin 5 mg/mL, Rotapharm, Monza, Italy), 100 µL of 2% agarose melted in phosphate-buffered solution (PBS) (Merck, Darmstadt, Germany), 50 µL of $CaCl_2$ at a concentration of 1% (Braun,

Kronberg, Germany), and 75 µL of Dulbecco's modified eagle medium (Merck) [22]. The patient's keratinocytes (100,000 cells/mL of stromal substitute) will be subcultured on top of the stromal substitute to generate an epithelial layer. Palate mucosa substitutes are generated on porous culture inserts to promote epithelial stratification and differentiation using the air–liquid culture technique as previously described [23,24]. Finally, the substitutes are subjected to plastic compression nanostructures to improve the biomechanical properties of the product, as described in previous studies [17]. This palate mucosa substitute will be applied to the denudated palatine bone on both sides of the palate defect and fixed using resorbable suture material.

Outcomes, measures, and variables

The clinical trial was designed with two preimplant visits (visits 1 and 2), one visit at the time of surgical repair of the palatal defect (visit 3), and nine postimplant evaluation visits (visits 4–12), with the last visit 24 months after uranostaphylorrhaphy (Figure 2).

- Preimplant visits: The first visit will occur when the child is approximately 12 months old (range, 10–14 months) according to the current follow-up and treatment protocols applied at the CMU. Patients will be evaluated at this visit, and patients satisfying all the inclusion criteria will be selected and recruited for the trial. Informed consent will be obtained from all the parents or caregivers of the patients. The second visit will confirm the patient's suitability for recruitment, and each patient will be randomly assigned to either the control or intervention group. The first five patients who meet the inclusion criteria will be assigned to phase I of the trial. The second visit will occur when the patient is 13–17 months old, approximately 30 days before uranostaphylorrhaphy.
- Implant visit (14–18 months of age): At the time of uranostaphylorrhaphy, with or without implantation of BIOCLEFT), the patient will be evaluated under general anesthesia. Before uranostaphylorrhaphy, the patient's palate cleft will be measured. The patient's head, face, mouth, and palate (craniomaxillofacial images) will be photographed, and palatal impressions in alginate gels will be obtained. These impressions will be used to generate 3D models of the patient's defects before surgical treatment. In addition, participants will be evaluated by a pediatric otorhinolaryngologist, and tympanostomy ventilation tubes will be implanted if necessary.
- Postimplant visits. The first two postimplant visits will occur 24 h and 48 h after uranostaphylorrhaphy when the patient is still at the hospital. During these visits, the patient's general condition and the surgical area of the palate will be evaluated. Specifically, the placement of the implant will be assessed, and short-term side effects and complications will be monitored, including graft detachment, bleeding, necrosis, infection, and other unexpected findings. Patients are routinely discharged 48h after surgery. The same parameters will be evaluated during the rest of the visits (visits 6 to 12), which will occur at 9 and 16 days and at 1.5, 4.5, 9, 15, and 24 months after discharge. The TNO-AZL Preschool Quality of Life (TAPQOL) questionnaire will be used to evaluate the patient's family at visits 7, 10, and 12, and a functional evaluation of the child's speech will be performed by a pediatric speech therapist at visit 11. If necessary, a pediatric otorhinolaryngologist will evaluate the patient at visits 8, 9, 10, 11, or 12.

As an initial clinical trial, the variables to be analyzed are mainly related to the feasibility of the procedure and the biosafety of the implant. However, secondary variables related to initial efficacy will be preliminarily analyzed, and the present trial will record some initial signs of implant efficiency. The following variables will be analyzed:

1. Primary outcome measures.
    a. Feasibility will be assessed using a questionnaire generated ad hoc for this trial that includes items related to the difficulties encountered during

the grafting process, macroscopic aspects, consistency, handling, and suturability of BIOCLEFT and other factors associated with the feasibility of the procedure (Supplementary Material S1).

b. Biosafety will be determined by analyzing the occurrence of serious and mild adverse or unexpected side events related to the implantation of BIOCLEFT, such as excessive bleeding, necrosis, infection, inflammation, or other local or systemic reactions that could be related to the implant.

2. Secondary outcome measures.

a. Effects of the implants on surgical site healing. The regeneration and healing of the palatine bone defects generated during uranostaphylorrhaphy will be analyzed by evaluating the surgical site at different time points.

b. Evaluation of aesthetic results. The appearance of the patient's head and face will be assessed by analyzing macroscopic photographs taken at different follow-up times. A specific aesthetic appearance assessment scale designed for children with OFC (Supplementary Material S2) will be used. This scale was designed based on previous scales used in children with cleft palate [25,26].

c. Preliminary evaluation of cranio-maxillofacial growth and development. Although the follow-up time of the present clinical trial is only 24 months, initial preliminary signs of the effects of the implant on craniomaxillofacial growth and development will be assessed by quantifying relevant measures and distances in the photographs and 3D models obtained from the patient at different time points.

d. Hearing evaluation. A pediatric otorhinolaryngologist will evaluate patients to detect any signs of hearing impairment or otologic defects. Once the otorhinolaryngologist has performed the initial hearing evaluation (preimplant visits), the need for follow-up postimplant visits will be assessed depending on whether the patient has any pathology.

e. Analysis of quality of life. The patients' families will be asked to fill out the TAPQOL questionnaire for children aged 1–5 years to determine if the treatment improved the quality of life of the patients' families. This questionnaire is widely used to analyze children's quality of life and contains several items evaluating 12 aspects of children's life, including sleeping, appetite, lungs, stomach, skin, motor functioning, communication, social functioning, behavioral problems, anxiety, positive mood, and liveliness [27,28].

f. Functional evaluation by a speech therapist. An expert pediatric speech therapist will determine whether the treatment influenced any relevant speech parameters, such as the ability to pronounce vowels and consonants, nasal escape, palate mobility, swallowing, and articulation of functional language. For this purpose, a 2–3 min conversational speech sample will be tape-recorded for further analysis, followed by a single-word articulation test to assess specific sounds. These tests evaluate the patient's ability to articulate speech and the resonance patterns associated with speech (hypernasality, resonance of specific vowels and consonants, detection of articulation errors).

After the trial, patients will be follow-up and treated in the CMU following the standard protocols established in this Unit.

Data sharing and diffusion plan

The results obtained from this trial will be posted in public databases and repositories as soon as possible as part of the study's data management plan. The results will be

published in a specialized journal. Personal data and those subject to special ethical or legal issues will be protected and not published. The data management plan is provided in Supplementary Material S3.

DISCUSSION

Despite the social and healthcare relevance of OFC, current treatments are still based on surgical techniques originally described many decades ago [29]. Although these techniques allow surgeons to generate a physical barrier between the oral and nasal cavities, the final outcomes of these patients remain suboptimal [6], and new treatments are needed. Among the most promising alternatives are advanced therapies using bioartificial tissues that offer the possibility of promoting tissue regeneration in patients with severe conditions [30].

Artificial tissues generated as ATMPs using TE increasingly demonstrate their potential clinical usefulness in diverse, complex pathologies. Moreover, artificial tissues have been successfully and safely used to treat patients with severe diseases [14,15,31,32]. However, the clinical translation of TE products is still limited, and little experience is available, especially for specific pathological conditions [33]. In addition, the regulatory frameworks associated with clinical translation are very complex, making using these products in humans challenging [34].

Following the successful clinical application of other human artificial tissues based on the same nanostructured fibrin–agarose biomaterials, we designed the present BIOCLEFT clinical trial [14,15]. As one of the first advanced therapy clinical trials applied to patients with OFC, the present trial was designed according to the requirements of the AEMPS as a phase I-IIa trial. In general, novel products, especially ATMPs, must be initially evaluated for biosafety, either in early-phase clinical trials or in the framework of hospital exemption and compassionate use [35,36]. For the BIOCLEFT clinical trial, we obtained authorization from the national regulatory agency in Spain instead of applying for hospital exemptions, as was done for a previous model of artificial skin generated by the group [35]. This will provide stronger scientific evidence of the effects of the artificial palate mucosa and enable future centralized marketing authorization in Europe without the restrictive conditions associated with hospital exemption [36].

As an early-phase clinical trial, the present study mainly focuses on establishing the feasibility of implanting the artificial palate mucosa and determining patient safety. Establishing feasibility is essential because the BIOCLEFT medical product is grafted onto the denudated areas of the palatine bone of patients affected by OFC during uranostaphylorrhaphy. Additionally, this is the first artificial tissue generated by TE containing two different cell populations (stromal and epithelial cells) generated as an ATMP and applied to patients with OFC. Therefore, this study primarily aims to demonstrate that the method and product are practically achievable. Although feasibility studies are common in cell therapy [37], few studies have described the feasibility of using human tissue generated by TW in clinical settings. Moreover, safety is among the most important requirements of new drugs and medicinal products [38], especially bioartificial tissues generated by TE [39].

This trial will also preliminarily analyze other parameters related to the clinical utility of the implant. However, given the short follow-up period in the present clinical trial (24 months post-implant follow-up), the efficacy between the control and intervention groups is unlikely to differ significantly. These preliminary results could be used to design future clinical trials in more advanced phases focused on determining the clinical efficacy of the palate mucosa substitutes generated by TE.

Regarding the analysis, biosafety will be analyzed by examining the patient's surgical site and evaluating the patient's general situation and clinical parameters. Based on our

previous experiences with other bioartificial tissues generated by TE [14,15], these analyses should be able to detect any possible side effects and complications effectively, both in the short and long term. Notably, the nanostructured fibrin–agarose artificial tissues previously generated by our research group typically show complete in vivo biointegration after one to three months [15,40]. To assess the preliminary efficacy of the bioengineered product, we will use a combination of methods, including analyzing the growth and development of the craniomaxillofacial structures, assessing the hearing ability of patients using otorhinolaryngology evaluation, analyzing speech ability, and using an established normalised questionnaire to evaluate the quality of life of children and their families [41]. This array of evaluation methods will provide researchers with a preliminary idea of the functional effects of the implant on the patient and will reveal the possible positive effects of the therapy, which should be confirmed by further analyses.

The BIOCLEFT clinical trial has several limitations. First, the study will be performed with a small number of participants, which is typically associated with lower statistical power [42]. However, initial biosafety studies usually include a small sample size, especially in ATMP studies. Moreover, the follow-up period may not be sufficient to identify the beneficial effects of the implant on the patient's craniomaxillofacial growth, development, and aesthetic appearance. If the present study demonstrates that the implant is feasible and safe for the patient, future advanced clinical trials should be conducted using longer follow-up periods to allow the patient's cranio-maxillofacial structures to grow and develop.

ETHICS AND DISSEMINATION

This study was approved by the Committee of Ethics in Research with Medicinal Products (CEIm), reference FIB-BIO-2023-03 (date of approval, November 21, 2023). As an advanced therapy study, the BIOCLEFT clinical trial was authorized by the Spanish Medicines Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS*), reference 2023-506913-23-00/ID:10008 (date of approval, November 21st, 2023). AEMPS will audit the development of the trial. The study was performed in compliance with the Declaration of Helsinki and the principles of Good Clinical Practice. All legal guardians signed an informed consent form before study entry (Supplementary Material S4). This clinical trial was registered at ClinicalTrials.gov (registration number NCT06408337). The results of the clinical trials will be published in a peer-reviewed journal.

AUTHOR CONTRIBUTIONS

AEL, RFV, EC, BQ, EA, GC, and MA conceived and designed the study. The clinical trial was conducted by all the authors, with AEL, RFV, AMP, DV, and ELL participating in the surgical procedures; IG, MAMP, VC, FC, JCA, ODGG, DSP, PAF, MEE, AC, and MA participated in the design and quality control of the medicinal product evaluated in the present work; and AEL, RFV, EC, BQ, EA, GC, and MA participated in the generation of the documents and protocols required for the clinical trial. AEL, RFV, and MA wrote the first version of the manuscript. IG, MAMP, VC and AC revised the manuscript and provided valuable information. M.A. is responsible for the overall content as guarantor. All the authors have read and approved the final version of the manuscript.

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Técnica y de Innovación 2017-2020), grant number ICI19/00024 (BIOCLEFT); supported by grants FIS PI21/00980 and PI24/00006, ISCIII, Spain; co-funded by the European Union, Fondo Europeo de Desarrollo Regional ERDF-FEDER. Funders play no role in the design and development of the study.

COMPETING INTERESTS

None declared.

DATA STATEMENT

This study was registered at ClinicalTrials.gov (NCT06408337) and EuclinicalTrials. gov (2023-506913-23-00). Results are not available yet.

PATIENT AND PUBLIC INVOLVEMENT

The patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this study.

PATIENT CONSENT FOR PUBLICATION

Not applicable.

FIGURE LEGENDS

Figure 1. Design of the BIOCLEFT clinical trial. The different phases and groups of patients are represented at each stage of the trial.

Figure 2. Stages of the BIOCLEFT clinical trial and investigations that will be conducted at each visit. The approximate moment when each visit will be programmed is shown to the left of the visit number, and the relevant analyses are represented with symbols (explained below the figure). PS: postsurgery. *Visit 2 will take place approximately 30 days before the surgical procedure.

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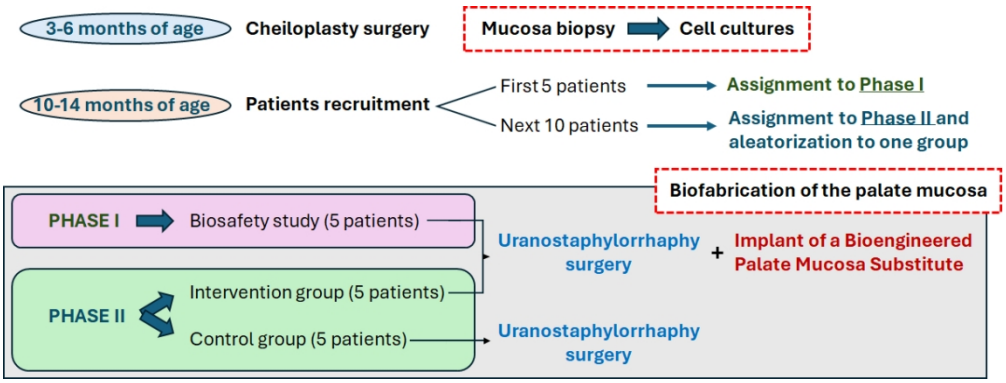

Figure 1

103x38mm (300 x 300 DPI)

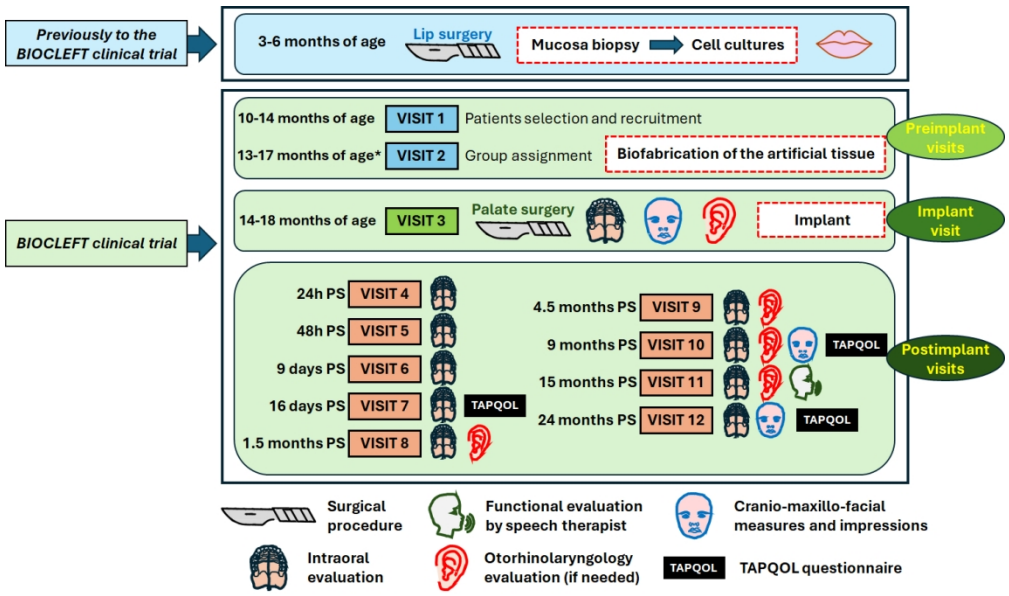

Figure 2

127x75mm (300 x 300 DPI)

Supplementary Table S1. Questionnaire used to assess feasibility of the procedure.

SURGEON SATISFACTION QUESTIONNAIRE. Each question must be rated using a Likert-like scale ranging from 1 to 5	VERY BAD (1)	BAD (2)	AVERAGE (3)	GOOD (4)	EXCELLENT (5)
1. GENERAL APPEARANCE AND ASPECT OF THE BIOCLEFT AUTOLOGOUS PALATE MUCOSA GENERATED BY TISSUE ENGINEERING USING NANOSTRUCTURED FIBRIN-AGAROSE BIOMATERIALS GRAFTED IN CHILDREN WITH CLEFT LIP AND PALATE					
1.1. The product has an adequate aspect, is homogeneous and is devoid of any apparent defects?					
1.2. The size of the product is adequate for use in patients affected by cleft lip and palate?					
1.3. The color of the product is compatible with a normal tissue?					
1.4. Is it easy to identify both tissue layers of the product (epithelium and connective tissue)?					
2. HANDLING THE BIOCLEFT PRODUCT					
2.1. Can this product be easily extracted from the recipient in which the tissue substitute has been delivered to the operating room?					
2.2. Can this product be easily handled using surgical forceps?					
2.3. Can this product be easily trimmed and adapted to the surgical site using a scalpel or other surgical instrument?					
2.4. Can this product be easily placed at the palate defect area?					
2.5. Can this product be easily sutured at the palate defect area?					
2.6. Has this product the capabiity to adhere to the palate defect area?					
3. RESULTS OF THE IMPLANT					
3.1. Has this product efficiently covered the palate defect area?					
3.2. Once grafted, is the aspect of the implant adequate?					
3.3. Once grafted, has the implant a homogeneous aspect, without bubbles and without any detectable defects?					
3.4. Overall, do you think the implant of the product has been feasible?					
3.5. In general, do you think the implant of the BIOCLEFT product has been easy?					

Supplementary Table S2. Questionnaire used to assess the patient's aesthetic appearance.

PATIENT AESTHETIC EVALUATION. Each question must be rated using a Likert-like scale ranging from 0 to 4	NO IMPROVEMENT (0)	25% IMPROVEMENT (1)	50% IMPROVEMENT (2)	75% IMPROVEMENT (3)	100% IMPROVEMENT (4)
1. LIP EVALUATION					
1.1. Lip symmetry					
1.2. Shape of the philtrum					
1.3. Visibility of the scar					
1.4. Symmetry of the dry/wet line					
1.5. Lip fullness					
2. NOSE EVALUATION					
2.1. Symmetry of the nose tip					
2.2. Symmetry of the nostrils					

FIBAO Fundación para la Investigación Biosanitaria de Andalucía Oriental. Alejandro Otero.

DATA MANAGEMENT PLAN (DMP)

Clinical trial title: Phase I-IIa, Randomized, Controlled, Open-label, Single-center Clinical Trial to Evaluate Safety, Feasibility, and Efficacy of the Use of BIOCLEFT in the Treatment of Patients with Cleft Palate (BIOCLEFT clinical trial)

Protocol number: FIB-BIO-2023-03

Sponsor: Fundación para la investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO)

Creator: Miguel Alaminos

Principal Investigators: Miguel Alaminos and Ricardo Fernández-Valadés

Affiliation: University of Granada and University Hospital Virgen de las Nieves, Granada, Spain

Template: DCC Template

ORCID iD: 0000-0003-4876-2672 (MA) and 0000-0001-8087-4311 (RFV)

Project abstract:

Introduction. Current gold-standard treatment for patients with orofacial cleft is the surgical repair of the palatal defect (uranostaphylorrhaphy), which is associated to growth defects and hypoplasia of the maxillofacial structures. This study will analyze the potential of a bioengineered model of artificial palate mucosa generated by tissue engineering using autologous stromal and epithelial cells and nanostructured fibrin-agarose biomaterials to improve the results of the treatment of patients with unilateral cleft palate and lip.

Methods and analysis. A phase I-IIa clinical trial was implemented to determine the feasibility and biosafety of a procedure in which a bioartificial palate mucosa is grafted on the areas of denudated bone in patients subjected to uranostaphylorrhaphy. Control patients will receive the standard surgical treatment. 5 patients will be included in the first biosafety phase of the study. A second phase will be implemented with 10 patients randomly assigned to the intervention or control groups (1:1). The intervention group will receive standard surgical treatment followed by application of an autologous bioartificial palate mucosa. Feasibility will be analyzed at the moment of surgery. 9 postimplant visits are scheduled in a 2-year follow-up period, in which local and systemic biosafety will be analyzed by determining the evolution of the graft (signs of necrosis, rejection, inflammation, etc.) and the patient. Preliminary signs of efficiency will be also explored by sequentially evaluating cranio-maxillo-facial development, hearing impairment, speech capability and the quality of life of the family. When available, results will be published in journals and posted in relevant repositories.

Ethics and dissemination. The study was approved by the Committee of Ethics in Research with Medicinal Products (CEIm) and authorized by the Spanish Medicines Agency (AEMPS). Results of the study will be published in peer-reviewed journals.

Trial registration. ClinicalTrials.gov: NCT06408337; Euclinicaltrials.eu: 2023-506913-23-00.

ID: 162342

Start date: 17-04-2024

Last modified: 27-10-2024

Grant number / URL: ICI19/00024

BIOCLEFT CLINICAL TRIAL

DATA COLLECTION

The data to be collected are described in the study protocol, and include:

- Participant information: ID, demographics, previous medical history.
- Inclusion/exclusion criteria.
- Treatment details.
- Outcome Measures (primary and secondary outcome data):
  - Feasibility data of the implant procedure.
  - Biosafety data of the implant procedure.
  - Effects of the implant on patient's growth, development and life quality.
  - Adverse events

The data collection process will be performed in a validated electronic Case Report Form (eCRF), by capturing data from participants enrolled in the study. Each participant's demographics, medical history, treatment details, and outcome measures will be entered in real time by trained site staff using an intuitive eCRF interface. Automated validation checks immediately flag any discrepancies, ensuring data accuracy from the outset. Regular source data verification will be conducted by the CRA to confirm that the data recorded aligns with the original documentation, maintaining compliance with regulatory standards.

DOCUMENTATION AND METADATA

As an advanced therapies clinical trial, the data will be accompanied by all the protocols and documents associated to this trial. The trial was approved by the Spanish Medicines Agency.

ETHICS AND LEGAL COMPLIANCE

As a clinical trial approved by the Spanish Medicines Agency, all legal issues are covered. The project has been approved by several ethics and research committees, including:

- Committee of Ethics in Research with Medicinal Products (CEIm) in Seville, reference FIB-BIO-2023-03 (date of approval, November 21th, 2023).
- Authorized by the Spanish Medicines Agency (*Agencia Española de Medicamentos y Productos Sanitarios, AEMPS*), reference 2023-506913-23-00/ID:10008 (date of approval, November 21st, 2023).

STORAGE AND BACKUP

As an advanced therapies clinical trial, the sponsor and the PIs will securely custody the data for at least twenty-five years following the completion of the trial.

Data will be preserved in digital form and custodied at the University Hospital Virgen de las Nieves, following all the security measures established for this type of studies, controlled by the clinical trial monitorization committee.

The PIs and the monitor are the only persons authorized to access the data. Other researchers could request partial access to the data.

DATA SHARING STATEMENT

Individual deidentified participant data will be shared, including data dictionaries, to promote transparency and further research in the field. The data shared will include demographic information, clinical outcomes and any adverse events reported during the trial. In addition to participant data, the following documents will be available: protocol and informed consent.

The results of the clinical trial will be made publicly available in the Clinical Trials Information System (CTIS) and on ClinicalTrials.gov. Since the trial is being conducted in Spain, it will adhere to the European regulations for the publication of results, which require that results be published within 12 months of trial completion. Additionally, the main

results and conclusions will be published in open-access journals and spread in scientific meetings and congresses to further disseminate our findings to the scientific community.

Non-personal data and data that are not considered to have ethical concerns or sensitive character will be deposited, whenever possible, in public repositories such as Zenodo or Digibug. Restrictions will affect the personal data and other data that could be sensitive or have ethical concerns.

RESPONSIBILITIES AND RESOURCES

Data management will be performed by the PIs of the project and the professionals in the Andalusian Network for the design and translation of Advanced Therapies participating in the clinical trial.

The data will be delivered using public repositories such as Zenodo or Digibug.

Junta de Andalucía

Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

INFORMATION SHEET FOR THE PARTICIPATION OF THE SUBJECT IN THE CLINICAL TRIAL AND INFORMED CONSENT BY REPRESENTATION

(THIS IS AN ENGLISH TRANSLATION OF THE ORIGINAL DOCUMENT WRITTEN IN SPANISH.

THE DOCUMENT IN SPANISH IS AVAILABLE AT THE END OF THIS DOCUMENT)

Title: A phase I-IIa unicenter, controlled, open and randomized clinical trial to evaluate the safety, feasibility, and preliminary efficacy of a human fibrin-agarose, nanostructured, palate mucosa substitute generated by tissue engineering for the treatment of children with cleft palate.

Protocol code: FIB-BIO-2023-03

Eu CT number: 2023-506913-23-00

Promoter: Fundación para la Investigación Biosanitaria de Andalucía Oriental - Alejandro Otero (FIBAO)

Principal Investigator: Ricardo Fernández Valadés

Center: Hospital Universitario Virgen de las Nieves

BACKGROUND

This document aims to inform you about a clinical trial, which is a research study to find better treatments for children with Cleft Lip and Palate, as it is the case of your child, and we invite you to participate.

The study has been approved by the Research Ethics Committee of Seville, which belongs to the Network of Ethics Committees of the Public Health System of Andalusia, and by the Spanish Medicines Agency, in accordance with current regulations regarding clinical trials with medicines, the European Regulation 536/2014, of April 16 and the Royal Decree 1090/2015, of December 4.

Our intention is that you receive the correct and sufficient information so that you can decide whether or not you want your child to participate in this trial. To do this, read this information sheet carefully and ask your doctor any questions you may have. You are also given a copy of this document so that you can evaluate it and consult it with the people you consider appropriate.

VOLUNTARY PARTICIPATION

We invite you to participate in the study because your child has a palate defect (total unilateral cleft lip and palate).

Your child's participation is voluntary, so you can decide not to participate. If you decide to give your consent and participate in the study, you may change your decision at any time, without altering your relationship with your doctor or causing any harm to the health care provided to your child.

WHAT DOES THE CLINICAL TRIAL CONSIST OF?

Cleft lip and palate are defects found in the upper lip, the roof of the palate, or both. They occur when these facial structures do not close completely during pregnancy and development. Cleft lip and palate entail functional and aesthetic alterations of various structures that, depending on the case, produce alterations in the pronunciation of words, swallowing, deformity of the lips, nose and palate, the musculature of the pharynx and the position of the teeth, as well as possible alterations in the emergence of temporary or permanent teeth, and the growth of facial bones

In order to repair these defects, quite complex interventions are performed to improve the aesthetic appearance and function of the facial structures and, depending on the case, to improve feeding, by preventing food from escaping through the nose, to improve pronunciation, and to favor the correct alignment of both dental arches. The complexity of the defect can lead to the operated area not to have a completely normal external appearance.

The artificial palate, called BIOCLEFT, is an advanced therapy medicinal product. It is made from cells donated by your own child and cultured, and natural materials: fibrin (a protein obtained from blood), and agarose (a natural product extracted from algae). By processing the previously donated sample, cell cultures of the two main types of cells that make up the palate will be obtained in the laboratory. Once these cells are expanded in the laboratory, they will be introduced into a fibrin-agarose matrix to generate the human artificial palate.

GOALS OF THE STUDY

The objective of the present study is to confirm that it is possible and safe to use a BIOCLEFT oral mucosa substitute generated from a sample of your child's own mucosa, and whether this use improves the aesthetic and functional results of current surgical treatment in relation to the closure of the cleft areas, and a more correct reconstruction in children affected by cleft lip and palate, as it is the case of your son/daughter.

STUDY DESCRIPTION

This is a clinical trial carried out in a single hospital.

Patients will be selected from children treated at the Cleft Lip and Palate and Craniofacial Malformations Care Unit (CLPU) of the Virgen de las Nieves University Hospital in Granada, and will be included in the study whenever they meet all the inclusion criteria, but not the exclusion criteria.

15 children affected by complete unilateral cleft lip and palate will participate in this study. All of them will undergo standard reconstruction surgery.

Of the 15 children, 10 patients will be treated with the standard reconstruction surgery, followed by covering the operated area with the novel product studied in this trial (experimental group), during the same surgical procedure, whereas the other 5 patients will receive only the standard reconstruction surgery.

The study will be carried out in 2 stages: the first 5 children to be included will all receive the study treatment. In a second stage, the remaining 10 children will have a 50% probability of receiving the investigational treatment and a 50% probability of receiving the standard treatment. Whether your child is assigned to the experimental group or to the control group, will depend on chance. You will be informed about the group assigned to your child.

Both surgical procedures will be performed under general anesthesia.

Children in both groups will receive the same usual reconstruction therapy and will undergo the same wound care, monitoring and evaluation protocol

An Independent Safety and Data Monitoring Committee has been established in the trial to analyze the results. Once the first 5 children have been treated, this Committee will decide, according to the data obtained, whether or not to continue with the inclusion of the remaining 10 patients.

The results of all your blood tests, as well as other analytical results, will be provided to the sponsor. These results are coded in such a way that the promoter will not know who owns these results. Positive results for HIV and viral hepatitis will be communicated to local health authorities as established by current regulations.

FOR HOW LONG SHALL I PARTICPATE IN THE STUDY?

Once you agree with the inclusion of your child in the study, your participation will last approximately 2 years. During this period, you will have to attend 12 visits: two visits before the standard surgical intervention and BIOCLEFT implant -if applicable-, one visit for the implant and 9 follow-up visits after the intervention.

The procedures that will be followed at each visit, as well as the number of visits, will be the same for all patients. The visit schedule is included in APPENDIX 1 to this document.

In addition to the visits described in the protocol, intermediate visits may be carried out if your doctor considers that these are needed.

RISKS AND DISCOMFORT ARISING FROM YOUR PARTICIPATION IN THE STUDY

Your participation in the study could be associated to several risks and discomforts that may arise from:

Participation in the Clinical Trial, since you and your child must attend all the visits listed in the protocol and in ANNEX 1, until the follow-up is completed.

Additionally, you will need to complete a series of clinical evaluations, and you will be asked to complete some questionnaires. In addition, in some of them, photographs of your child's face and molds of the dental arch will be taken, to check the evolution. Finally, the blood analyses that will be performed at the beginning of the study carries a minimal risk, and may cause discomfort such as pain and slight hematoma (accumulation of blood in the skin) in the puncture area.

To assess the aesthetic appearance and the changes that occur in response to the treatment, photographs of your child's head (face and skull) will be taken at different visits (Visit 1, 3, 10 and 12). These photographs

will be studied by an expert surgeon and may later be used in scientific publications. In the photograph, the eye area with the black spot will be hidden to avoid facial recognition of the patient.

The risks derived from surgery are common to the control group and the experimental group. Despite the correct surgical technique, undesirable effects derived from the intervention may occur:

- Frequent non-serious risks depend on the degree of alteration present in the lip, and the condition of the patient, and include: Hemorrhage or infection of the surgical wound, healing problems, separation of the edges of the wound or appearance of fistulas between the mouth and nose, asymmetry of the nose and lip contour, difficulty in pronouncing some sounds and finally, impossibility of complete closure.
- The most serious and rare risks that may occur include: Necrosis of any of the areas of the skin that is used to close the fissure of the palate, lip or nose. Although these complications may occur, complications derived from the use of operating materials (electric scalpel, thermal blanket, etc.) or postural complications are very rare.
- Other risks related to the anesthesia used: The anesthetic risk depends on many factors such as the type and severity of the pathology that motivates the operation, whether it is performed urgently, other diseases suffered by the patient, or his/her condition or age. All these parameters may increase side effects. The most common include: nausea and vomiting, throat conditions in case of intubation; vertigo and vision disorders, tremors, headache, itching, muscle and joint pain and back pain. In the hours following anesthesia, temporary disorders of memory, attention or behavior of the child may appear. The most serious are: aspiration of stomach contents into the lungs, although this is very rare if preoperative fasting has been respected, unforeseeable complications that could endanger your child's life such as a true allergic reaction, malignant hyperthermia (fever), respiratory failure or cardiac arrest. Death during anesthesia is very rare and is almost always the consequence of a set of simultaneous complications.

Risks derived from the investigational medical product:

To date, no toxic effects have been described due to the administration of the elements used to generate the artificial mucosa, including fibrin, agarose and oral mucosa cells. This does not exclude the possibility that some problems may occur. As it is an investigational treatment, this is one of the aspects to be assessed from a safety point of view.

The medication may contain traces of Gentamicin and Amphotericin B derived from the manufacturing process. If you know that your child is allergic to these medications, you should inform the medical personnel in charge of the intervention.

All necessary tests and treatments will be carried out so that the risks of the intervention and evaluation tests are reduced to a minimum.

WHAT ARE THE EXPECTED BENEFITS?

Based on current scientific evidence, it is expected that the proposed treatment will improve the repair of the clefted tissues and, as a consequence, your child may have an appearance similar to that of any other child who was not born with the injury, as well as the improvement of certain functions such as speech, swallowing, hearing, etc.

In any case, with your participation in the study you will contribute to improving knowledge about possible alternatives to treat this disease, thus collaborating in the scientific advancement of society.

WHAT IS MY COMMITMENT?

You agree to attend the visits with your child and undergo the scheduled tests, to notify any adverse event that happens to your child, whether or not it is related to the clinical trial, and to communicate any changes made to your child's medication, if any. If you stop attending follow-up visits without having expressly revoked your consent, the sponsor may complete your clinical follow-up by accessing your medical history at the center and collecting data for the study.

Likewise, you must inform the different health professionals with whom you have a relationship that your child is participating in this clinical trial, warning them that, for safety reasons and possible contraindications with the investigational product. Current medication should not be modified without consulting the study doctor in the event that your child has any prescribed medication.

IF I HAVE ANY QUESTIONS OR QUESTIONS, WHO CAN I CONTACT?

You can **ask any questions you want** and learn more about this clinical trial, **now or at any time** during the course of the trial. Additionally, if you notice your child experiencing any adverse events, you should contact the study doctor immediately.

Study researcher: Dr. Ricardo Fernández Valadés.

Phone: .....

E-mail: .....

Hospital: Hospital Universitario Virgen de las Nieves

If you need emergency medical attention, you can go to your child's usual center. You must inform the different health professionals with whom you have a relationship that you are participating in this clinical trial and provide all possible them with information related to the study.

WHAT ALTERNATIVE TREATMENTS ARE THERE?

It is important that you know that if you do not want your child to participate in the proposed clinical trial, the researcher responsible for the development of the clinical trial will indicate the palliative or curative alternatives currently available for the management of the disease.

Do not hesitate to consult with the researcher responsible for the development of the clinical trial if you have any questions or if you need any clarifications on this issue.

EXPENSES AND ECONOMIC COMPENSATION

The Promoter of the study is in charge of the economic aspects of the study. To carry out the study, the Public Foundation FIBAO has signed the corresponding contract for its implementation. This is a clinical trial carried out within the public system. Neither the center nor the research team will receive any financial compensation. Your participation in the study will not entail any additional expense to the usual clinical practice of your disease.

WHAT TREATMENT WILL I RECEIVE WHEN MY PARTICIPATION IN THE STUDY WILL FINISH?

Once your participation in the study ends, your child will receive the treatment that his/her doctor considers most appropriate for his/her clinical situation.

INSURANCE POLICY

The Promoter of the study has an insurance policy that complies with current legislation (Royal Decree 1090/2015), which will provide compensation in the event of impairment of the health of your child or injuries that may occur related to his/her participation in the study, as long as these events are not a consequence of the disease itself or its evolution as a consequence of the ineffectiveness of the treatment. This policy has been contracted with the insurance company HDI Global. For more information regarding this section, please consult the principal investigator of the study at your center.

WHO HAS ACCESS TO MY DATA?

Both the promoter and the center will ensure that the principles contemplated in the data protection regulations, both national and European, are complied with.

For more information on confidentiality and protection of personal data, see APPENDIX 1.

WHAT IS MY DATA USED FOR?

Your data is necessary for the sponsor to develop the medicinal product, to obtain permission to introduce and keep it on the market, monitor its safety, and cover it with health insurance, that is, throughout the drug development program. Therefore, they will be used as planned in this study, as well as within the related research activities necessary for this drug development program in order to:

- understand how the study product and similar drugs work in the body (that is, evaluate the mode of action of the study product),
- better understand the studied disease and associated health problems,

- develop diagnostic tests for the disease,
- learn from this study to plan new studies or improve scientific analysis methods,
- publish research results in scientific journals or use them for educational purposes.

OTHER RELEVANT INFORMATION

A description of this clinical trial will be available at **http://reec.aemps.es as** required by Spanish legislation. You will also find information about the study at **https:// https://clinicaltrials.gov**. In addition, one year after the end of the study, a summary of its results (regardless of what they are) will be available in the European Union database, as well as a summary written in a language understandable to a person.

Any new information regarding the therapies used in the study that may affect your willingness for your child to participate in the study, which is discovered during your participation, will be communicated to you by your doctor as soon as possible.

If the new information implies any modification to the information sheet, you will be provided with the new version of the document, giving you the opportunity to decide if you want your child to continue participating in the study

WHEN WILL MY PARTICIPATION IN THE TRIAL END?

The investigator, the Sponsor, the Ethics Committee and the regulatory authorities that supervise this clinical trial may decide to withdraw your child from the study if they consider that it will be for your best interest.

- Once the **follow-up period has concluded**, which will last approximately 24 months, from signing the consent.
- **At any time if you decide**, you must notify the researcher.
- If the **study doctor decides to suspend your child's participation** in the trial, because a new medication with greater proven effectiveness has been approved, because he/she considers it to be the best for your child, or if you do not follow the procedures of the study clinical trial, you will receive an adequate explanation of the reason that caused your child to withdraw from the study.
- For **other unforeseen circumstances**, whenever the Promoter or the Health Authorities consider it appropriate.

In any case, you must follow the instructions given to you by the study doctor for an orderly completion of the trial.

WHAT WILL HAPPEN TO MY SAMPLES?

The blood samples collected will be associated with a code that can only be related to your child's identity and medical history by the study doctor/collaborators. The data derived from the use of these samples will be treated in the same way as the rest of the data obtained during the test. Your samples and associated data may be analyzed in various laboratories, for the same purposes of the study described, but always maintaining the confidentiality of your identity in accordance with current legislation.

ACKNOWLEDGEMENT

Whatever your decision is, the sponsor and research team would like to thank you for your time and attention.

Junta de Andalucía

Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

PARTICIPANT CONSENT SHEET BEFORE WITNESSES AND/OR RELATIVES OR RELATIVES

Title of the study: A phase I-IIa unicenter, controlled, open and randomized clinical trial to evaluate the safety, feasibility, and preliminary efficacy of a human fibrin-agarose, nanostructured, palate mucosa substitute generated by tissue engineering for the treatment of children with cleft palate

Protocol code: FIB-BIO-2023-03 **Eu CT number:** 2023-506913-23-00

I,_____<<*name of the parent or legal guardian*>>, as

☐ Father/Mother / ☐ Legal guardian,

I declare that I received a satisfactory explanation on the study procedure, its objectives, risks, benefits and alternatives, from Dr.:

_____ <<*name of the researcher*>>, and I have read the study information sheet that has been provided to me, and:

☐ I had the opportunity to make any questions on the study

☐ I have received enough information on the study

☐ I have been speaking with

_____ <<*name of the researcher*>>

☐ I understand that my participation is voluntary

☐ I understand that I can withdraw from the study:

- Whenever I wish,
- Without the need of giving any explanations
- Without any consequences of the care and treatment provided to my son/daughter

The participant accepts taking any biological simples for the objectives of the study:

☐ YES ☐ NO

The parents or legal guardian of the participant in the study wishes to be informed about any information derived from the study that may be relevant to his/her health:

☐ YES ☐ NO

I will receive a signed and dated copy of this informed consent document.

I freely give my consent for my child to participate in the study.

Signature of one of the parents or legal guardians: Date: Name and original written signature	Signature of the research and ID number: Date: Name and original written signature

Signature of another of the parent or legal guardian: Date: Name and original written signature	Signature of the research and ID number: Date: Name and original written signature

Junta de Andalucía

Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

APPENDIX 1. Personal data protection related to the Patient Information Sheet and Informed Consent documents of the study

Title of the study:	A phase I-IIa unicenter, controlled, open and randomized clinical trial to evaluate the safety, feasibility, and preliminary efficacy of a human fibrin-agarose, nanostructured, palate mucosa substitute generated by tissue engineering for the treatment of children with cleft palate.
Code of the study:	FIB-BIO-2023-03
EU CT Number:	2023-506913-23-00
Promoter:	Fundación para la Investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO)
Principal Investigator:	Ricardo Fernández Valadés
Center:	Hospital Universitario Virgen de las Nieves

In accordance with the provisions of Regulation (EU) 2016/679 of the European Parliament and the European Council of April 27, 2016 on Data Protection and the Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights, it is important that you know the following information:

The Foundation for Biosanitary Research of Eastern Andalusia - Alejandro Otero (FIBAO) is the promoter of this study. It is based in Granada. Both the Center and the Promoter are responsible for their respective treatments, with each of them corresponding to the obligations derived from their activity. The center is responsible for all the data that appear in the medical record that can identify you, whilst the promoter is responsible for data that are collected in this study in a coded way. During your participation in the study, you will be identified by a code and neither the researcher nor the hospital will transfer to the sponsor any information that could directly identify you.

The list that relates the identification code and the data that identifies you (name, surname, medical record number...) is kept confidentially at your health center.

WHAT HAPPENS WITH CONFIDENTIALITY?

Access to your identified personal information will be restricted to the study doctor and collaborators, health authorities (Spanish Medicines Agency, foreign health authorities), the Ethics Committee for Research with Medicines (CEIm) and personnel authorized by the promoter (study monitors or auditors), when it is needed to verify the data, study procedures, and compliance with standards of good clinical practice, but always maintaining confidentiality. Your child's identity may be revealed in exceptional cases, such as medical emergencies for his/her health or legal requirements. Processing, communication and transfer of personal data of all participants will comply with the provisions of the applicable regulations.

Likewise, in the event of an adverse reaction, the identifying data may be communicated by the Center to the competent health authorities and to the insurance companies with which insurance has been contracted, in order to carry out the necessary steps.

The encrypted data may be transmitted to third parties and other countries, but in no case will it contain information that can directly identify your child, such as name and surname, initials, address, social security number, etc. In the event that this transfer occurs, it will be for the same purposes of the study described or for use in scientific publications, but always maintaining their confidentiality in accordance with current legislation.

FOR HOW LONG WILL MY DATA BE KEPT?

The Researcher and the Sponsor are obliged to retain the data collected for the study for at least 25 years after its completion. Afterwards, your personal information will only be maintained by your child's health care facility.

WHAT RIGHTS DO I HAVE?

With respect to the data, your child has the following rights that you may exercise before the main researcher and/or center:

- You can ask at any time what data are stored (right of access), who is using these data and for what purpose; you may request a copy of the personal data for your own use.
- You can request to receive a copy of the personal data provided by you to transmit these data to other people (portability).
- You can correct your child's personal data provided by you and limit the use of data that are incorrect (right of rectification and deletion).
- You can object to the use of personal data or restrict this use (right to object).

We remind you that there are some limitations in order to ensure the validity of the research and comply with the legal duties of the sponsor and drug authorization requirements. If you decide that your child stops participating in the trial or withdraws your consent to data processing, the data collected up to that point cannot be deleted. You should know that if you decide to withdraw consent regarding data processing, it could determine your termination of participation in the trial.

WHO CAN I CONTACT?

To exercise your rights, contact the principal investigator of the study (whose details appear on the information sheet above) or the Data Protection Officer of your Center, or the promoter.

Data Protection Delegate for all centers of Junta de Andalucía:

Email: dpd.sspa@juntadeandalucia.es

Data Protection Delegate for the promoter:

Email: dpd.csalud@juntadeandalucia.es

Likewise, you have the right to contact the Data Protection Agency if you are not satisfied (through the website *www.aepd.es*).

HOW WILL THE RESULTS BE COMMUNICATED?

A description of this clinical trial will be available at https://reec.aemps.es, as required by Spanish legislation.

The sponsor is obliged to publish the results, both positive and negative, of authorized clinical trials, preferably, in scientific journals before being disclosed to the non-specialized public, regardless of the obligations to publish the report of the results in the Spanish Registry of clinical studies (REec) and the provisions established in this regard in Regulation (EU) No. 536/2014 of the European Parliament and the European Council, of April 16, 2014.

When studies and research work on medicines are made public, aimed at the scientific community, the funds obtained by the author, for its development, and the source of financing, will be stated.

The anonymity of the subjects participating in the trial will be maintained at all times.

SAFEGUARD FOR THE PROTECTION OF YOUR PERSONAL DATA

Appropriate protective measures will be taken to protect encrypted data during and after the test, including:

- Access to encrypted data will be limited to persons subject to confidentiality obligations (including the obligation not to attempt to re-identify patients or decode clinical data).
- Encrypted data will be protected with security measures to prevent alteration, loss and unauthorized access and additional measures may be applied to prevent identification.
- Encrypted data will not be shared for direct marketing purposes or for other purposes that are not legal obligations or are not considered scientific research in accordance with current data protection legislation. In particular, they will not be used to make decisions about future services that may be offered to you, such as insurance.

Junta de Andalucía

Consejería de Salud y Consumo
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ANNEX 1. CALENDAR OF VISITS AND PROCEDURES

Visit	Procedures and evaluations
V1 Selection. 4 months before the surgical procedure	□ Informed consent signature □ Obtaining blood samples and photographs; Quality of Life Questionnaire.
V2 (by phone). 1 month before the surgical procedure	□ To confirm that you can be included in the study, and that a group can be assigned to you.
V3. Surgical procedure	□ Surgical procedure □ Evaluation by the ENT doctor, obtaining molds and photographs.
V4, 5 & 6. 1, 2 and 7 days after the surgical procedure	□ Wound evaluation, including photographs
V7. 14 days after the surgical procedure	□ Wound evaluation, Quality of Life questionnaire and photographs
V8 & V9. 1.5 and 4 months after the surgical procedure	□ Wound evaluation and evaluation by the ENT doctor, if necessary.
V10. 9 months after the surgical procedure	□ Evaluation, palate impressions and generation of molds and photographs. Evaluation by the ENT doctor if necessary. Quality of life questionnaire
V11. 15 months after the surgical procedure	□ Wound evaluation. Language assessment by the speech therapist. Obtaining photographs
V12. 24 months after the surgical procedure	□ Wound evaluation. Quality of life questionnaire, photographs. Evaluation by the ENT doctor if necessary, and language assessment by the speech therapist.

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Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

HOJA DE INFORMACIÓN PARA LA PARTICIPACIÓN DEL SUJETO EN EL ENSAYO CLÍNICO Y CONSENTIMIENTO INFORMADO POR REPRESENTACIÓN

Título: Ensayo clínico fase I-IIa, aleatorizado, controlado, no enmascarado y unicéntrico, para evaluar la seguridad, factibilidad e indicios de eficacia del uso de un sustituto autólogo de mucosa palatina humana de fibrina-agarosa nanoestructurada generado por ingeniería tisular, en el tratamiento de pacientes con fisura palatina.

Código protocolo: FIB-BIO-2023-03

Eu CT number: 2023-506913-23-00

Promotor: Fundación para la Investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO)

Investigador Principal: Ricardo Fernández Valadés

Centro: Hospital Universitario Virgen de las Nieves

INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un ensayo clínico, que es un estudio de investigación para poder encontrar mejores tratamientos para niños con Fisura Labio Palatina, como la que presenta su hijo, en el que le invitamos a participar.

El estudio ha sido **aprobado** por el Comité de Ética de la Investigación con medicamentos de Sevilla, que pertenece a la Red de Comités de Ética del Sistema Sanitario Público de Andalucía, y por la Agencia Española de Medicamentos y Productos Sanitarios, de conformidad con la legislación vigente en materia de ensayos clínicos con medicamentos, el Reglamento Europeo 536/2014, de 16 de abril y el Real Decreto 1090/2015, de 4 de diciembre.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir **si quiere o no que su hijo/a participe** en este ensayo. Para ello, lea esta hoja de información con atención y pregunte a su médico las dudas que le puedan surgir. Se le entrega, además, una copia de este documento para que pueda valorarlo y consultarlo con las personas que considere oportuno.

PARTICIPACIÓN VOLUNTARIA

Le invitamos a participar en el estudio porque su hijo/a presenta una lesión en el paladar consistente en una fisura unilateral total.

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La **participación de su hijo/a es voluntaria**, por lo que puede decidir no participar. Si decide otorgar su consentimiento y que su hijo/a participe en el estudio, podrá cambiar su decisión en cualquier momento, sin que por ello se altere la relación con su médico, ni se produzca perjuicio alguno en su atención sanitaria.

¿EN QUÉ CONSISTE EL ENSAYO CLÍNICO?

Las fisuras del labio y del paladar son orificios o hendiduras del labio superior, del techo del paladar, o de ambos. Se producen cuando estas estructuras de la cara no se cierran por completo durante el embarazo. La fisura labio-palatina conlleva alteraciones funcionales y estéticas de varias estructuras que, según los casos, producen alteraciones de la pronunciación de las palabras, al tragar, deformidad de labios, nariz y paladar, de la musculatura de la faringe y de la posición de los dientes, así como posibles alteraciones en la salida de los dientes temporales o definitivos, y del crecimiento de los huesos de la cara.

Para cerrar estas fisuras se realizan intervenciones que son bastante complejas, y que están destinadas a mejorar el aspecto estético y la función, y según los casos la mejora de la alimentación, evitar la salida de comida por la nariz, mejora de la pronunciación, y el correcto alineamiento de ambas arcadas dentarias. La complejidad puede hacer que el aspecto exterior de la zona operada no sea totalmente normal.

Este paladar artificial, que llamamos BIOCLEFT, es un medicamento de terapia avanzada. Está elaborada a partir de células donadas por su propio hijo/a, en cultivo y materiales naturales: fibrina (proteína obtenida de sangre), y agarosa (producto natural extraído de algas). Mediante el procesamiento de la muestra donada previamente, se obtendrán en el laboratorio cultivos celulares de los dos tipos de células que conforman el paladar. Una vez multiplicadas estas células en el laboratorio serán introducidas en una matriz de fibrina y agarosa para fabricar el paladar artificial humano.

OBJETIVO DEL ESTUDIO

El **objetivo** del presente estudio es confirmar que es posible y seguro utilizar un sustituto de mucosa oral, BIOCLEFT, fabricado a partir de una muestra de la propia mucosa de su hijo/a, y si este uso mejora los resultados estéticos y funcionales del tratamiento quirúrgico habitual, en relación con el cierre de las zonas fisuradas, y una reconstrucción más correcta, en los niños/as que, como su hijo/a, presentan una fisura del labio y del paladar.

DESCRIPCIÓN DEL ESTUDIO

Se trata de un ensayo clínico que se realizará en un único hospital.

Los pacientes serán seleccionados de entre los que acudan a la Unidad de Cuidados de labio Leporino y paladar hendido y malformaciones craneofaciales (CLPU) del Hospital Universitario Virgen de las Nieves de Granada. y se incluirán en el mismo, siempre que cumplan todos los criterios de inclusión y ninguno de exclusión.

En este estudio participaran 15 niños, afectados de fisura labial y palatina completa unilateral. Todos ellos serán sometidos a la cirugía de reconstrucción habitual.

De los 15 niños, en 10 de ellos, en la misma intervención de la cirugía de reconstrucción habitual, la zona operada se recubrirá con el medicamento que se está estudiando (grupo experimental) y los otros 5 recibirán solamente la cirugía de reconstrucción habitual.

El estudio se realizará en 2 etapas: los 5 primeros niños que se incluyan, recibirán todos ellos el tratamiento en estudio. En una segunda etapa, los 10 niños restantes, tendrá una probabilidad del 50% de recibir el tratamiento en investigación y una probabilidad del 50% de recibir el tratamiento estándar. El que a su hijo/a le corresponda el grupo experimental o el grupo control, dependerá del azar. Usted sabrá en qué grupo le ha tocado participar.

Ambos procedimientos quirúrgicos se realizarán bajo anestesia general.

Los niños de ambos grupos recibirán la misma terapia de reconstrucción habitual y serán sometidos a un mismo protocolo de cuidado de la herida, seguimiento y evaluación.

En el ensayo se ha establecido un Comité Independiente de Seguridad y Monitorización de Datos para analizar los resultados que se vayan produciendo, y este Comité, una vez tratados los 5 primeros niños, según los datos obtenidos, decidirá si se continua o no con la inclusión de los 10 pacientes restantes.

Se facilitarán al promotor los resultados de todos sus análisis de sangre, así como otros resultados analíticos. Estos resultados están codificados de manera que el promotor no sabe a quién pertenecen dichos resultados. Los resultados positivos del VIH y de la hepatitis viral se comunicarán a las autoridades sanitarias locales tal como marca la legislación sanitaria.

¿CUÁNTO DURARÁ MI PARTICIPACIÓN EN EL ESTUDIO?

Una vez que usted acepte que su hijo/a participe en el estudio, su participación durará aproximadamente 2 años. Durante este periodo deberá acudir a 12 visitas: dos visitas antes de la intervención quirúrgica estándar e implante de BIOCLEFT, si le corresponde, una visita para el implante y 9 visitas de seguimiento tras la intervención.

Los procedimientos a seguir en cada visita, así como el número de visitas serán los mismos para todos los pacientes. El calendario de las visitas se recoge en el ANEXO 1 a este documento.

Además, de las visitas descritas en el protocolo, se podrán realizar todas las visitas intermedias que el médico responsable considere oportuno.

RIESGOS Y MOLESTIAS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Su participación en el estudio podría ocasionar un conjunto de riesgos e incomodidades que se pueden derivar de:

La participación en el Ensayo Clínico, ya que usted y su hijo/a deberán atender a todas las visitas recogidas en el protocolo y en el ANEXO 1, hasta completar el seguimiento.

Además, será necesario realizar una serie de evaluaciones clínicas y se le pedirá que complete algunos cuestionarios. Además, en algunas de ellas se tomarán fotografías de la cara y moldes de la arcada dentaria de su hijo/a, para ir comprobando la evolución. Por último, la extracción de sangre que se realizará al inicio del estudio conlleva un riesgo mínimo, pudiendo producir molestias como dolor y hematoma leve (acúmulo de sangre en la piel) en la zona de punción.

Para valorar la apariencia estética y los cambios que se vayan produciendo en respuesta al tratamiento, se le realizarán a su hijo/a, fotografías de la cabeza (cara y cráneo), en diferentes visitas (Visita 1, 3, 10 y 12). Estas fotografías serán estudiadas por un cirujano experto, y podrán ser empleadas posteriormente en publicaciones científicas. En la fotografía se ocultará la zona de los ojos con mancha negra para evitar el reconocimiento facial del paciente.

Los riesgos derivados de la cirugía son comunes al grupo control y al grupo experimental. A pesar de la correcta técnica quirúrgica pueden presentarse efectos indeseables derivados de la intervención:

- Los riesgos frecuentes y no graves dependen del grado de alteración presente en el labio, y del estado del paciente, son: Hemorragia o infección de la herida quirúrgica, problemas de cicatrización, separación de los bordes de la herida o

aparición de fístulas entre la boca y la nariz, asimetría de la nariz y del contorno del labio, dificultad para la pronunciación de algunos sonidos y por último imposibilidad de cierre completo.

- Los riesgos más graves e infrecuentes que pueden darse son: Necrosis de alguna de las zonas de la piel que se utiliza para cerrar la fisura del paladar, del labio o de la nariz; pueden ocurrir, pero son muy infrecuentes las complicaciones derivadas del uso de material de quirófano (bisturí eléctrico, manta térmica, etc.) o las complicaciones posturales.

- Otros riesgos son los relacionados con la anestesia empleada: El riesgo anestésico depende de muchos factores como son el tipo y la gravedad de la patología que motiva la operación, si se realiza de urgencia, otras enfermedades que padezca el/la paciente, o su edad, puede aumentar los efectos secundarios. Los más frecuentes son: náuseas y vómitos, afecciones en la garganta en caso de intubación; vértigos y trastornos de la visión, temblores, dolor de cabeza, picores, dolores musculares, articulares y dolor de espalda. En las horas que siguen a la anestesia pueden aparecer trastornos pasajeros de memoria, de la atención o del comportamiento del niño. Los más graves son: paso del contenido del estómago a los pulmones, aunque es muy raro si se ha respetado el ayuno preoperatorio, complicaciones imprevisibles que puedan poner en peligro la vida de su hijo como una reacción alérgica verdadera, una hipertermia (fiebre) maligna, insuficiencia respiratoria o una parada cardiaca. La muerte en el curso de una anestesia es muy rara y casi siempre es la consecuencia de un conjunto de complicaciones simultáneas.

Riesgos derivados de medicamento en investigación:

Hasta el momento no se han descrito efectos tóxicos por la administración de los elementos usados para la fabricación de la mucosa artificial, como son la fibrina, la agarosa y las células de la mucosa oral. Esto no significa que no pudiera producirse alguno. Al tratarse de un tratamiento en investigación, éste es uno de los aspectos a valorar desde el punto de vista de seguridad.

El medicamento puede contener trazas derivadas del proceso de fabricación de Gentamicina y de Anfotericina B. Si usted conoce que su hijo presente alergia a estos medicamentos, debe ponerlo en conocimiento del personal facultativo encargado de la intervención.

Se harán todas las pruebas y tratamientos necesarios para que los riesgos de la intervención y de las pruebas de evaluación se reduzcan al mínimo.

¿CUÁLES SON LOS BENEFICIOS ESPERADOS?

Basándonos en la evidencia científica, se espera que el tratamiento propuesto mejore el cierre de las zonas fisuradas y como consecuencia que su hijo/a presente un aspecto parecido al de cualquier otro niño que no haya nacido con la lesión, así como la mejora de ciertas funciones como son el habla, la deglución, audición, etc.

En cualquier caso, con su participación en el estudio contribuirá a mejorar el conocimiento sobre posibles alternativas para tratar su enfermedad, colaborando de este modo en el avance científico de la sociedad.

¿CUÁL ES MI COMPROMISO?

Usted se compromete a **acudir junto con su hijo/a a las visitas y a que se someta a las pruebas programadas,** notificar cualquier **evento adverso** que le suceda a su hijo/a, tenga o no relación con el ensayo clínico y a comunicar los **cambios realizados en su medicación,** si los hay. En caso de que deje de acudir a las visitas de seguimiento sin haber revocado expresamente su consentimiento, el promotor podrá completar su seguimiento clínico mediante el acceso a su historial médico en el centro y recogida de datos para el estudio.

Asimismo, deberá **comunicar a los distintos profesionales de la salud** con los que tenga relación que su hijo/a está participando en este ensayo clínico, advirtiéndoles que, por motivos de seguridad y posibles contraindicaciones con el medicamento en investigación, no deben modificar la medicación que esté tomando sin consultar antes con el médico del estudio en el caso de que tenga medicación prescrita.

SI TENGO ALGUNA DUDA O CONSULTA, ¿A QUIÉN ME DIRIJO?

Puede **realizar todas las preguntas que desee** y saber más sobre este ensayo clínico, **ahora o en cualquier momento** en el curso del mismo. Además, si observa que su hijo/a experimenta cualquier **evento adverso**, debe contactar inmediatamente con el médico del estudio.

Investigador del estudio: D. Ricardo Fernández Valadés.

Teléfono: ……

Email: ……

Hospital: Hospital Universitario Virgen de las Nieves

En caso de necesitar atención médica de urgencia puede dirigirse al centro habitual de su hijo/a, deberá **comunicar a los distintos profesionales de la salud** con los que tenga relación que está participando en este ensayo clínico y facilitar toda la información posible relativa al estudio.

¿QUÉ TRATAMIENTOS ALTERNATIVOS EXISTEN?

Es importante que sepa que en caso de no querer que su hijo/a participe en el ensayo clínico que se le propone, el investigador responsable del desarrollo del ensayo clínico le indicará las alternativas paliativas o curativas actualmente disponibles para el manejo de su enfermedad.

No dude en consultar con el investigador responsable del desarrollo del ensayo clínico cualquier duda que tenga o si necesita cualquier aclaración sobre esta cuestión.

GASTOS Y COMPENSACIÓN ECONÓMICA

El Promotor del estudio gestiona los aspectos económicos del mismo. Para la realización del estudio la Fundación Pública Andaluza para la Investigación Biosanitaria en Andalucía Oriental- Alejandro Otero ha firmado el correspondiente contrato para su realización. Se trata de un ensayo clínico realizado dentro del sistema público. Ni el centro ni el equipo investigador recibirán compensación económica alguna. Su participación en el estudio no le supondrá ningún gasto adicional a la práctica clínica habitual de su enfermedad.

¿QUÉ TRATAMIENTO RECIBIRÉ CUANDO FINALICE MI PARTICIPACIÓN EN EL ESTUDIO?

Una vez finalice su participación en el estudio, su hijo/a recibirá el tratamiento que su médico considere más adecuado para su situación clínica.

PÓLIZA DE SEGURO

El Promotor del estudio dispone de una póliza de seguros que se ajusta a la legislación vigente (Real Decreto 1090/2015), que le proporcionará la compensación e indemnización en caso de menoscabo de la salud de su hjo/a o de lesiones que pudieran producirse en relación con su participación en el estudio, siempre que no sean consecuencia de la propia enfermedad que se estudia o de la evolución propia de la misma como consecuencia de la ineficacia del tratamiento. Dicha póliza, ha sido contrata con la compañía aseguradora **HDI Global**. Si desea más información relativa a este apartado, consulte con el investigador principal del estudio en su centro.

¿QUIÉN TIENE ACCESO A MIS DATOS?

Tanto el promotor como el centro se asegurarán de que se cumplan los principios contemplados en la normativa de protección de datos, tanto nacional como europea

Para obtener más información sobre la confidencialidad y la protección de datos de carácter personal, consulte el Apéndice 1.

¿PARA QUÉ SE UTILIZAN MIS DATOS?

Sus datos son necesarios para que el promotor desarrolle el medicamento, obtenga permiso para introducirlo y mantenerlo en el mercado, supervise su seguridad y lo cubra el seguro de salud, es decir, durante todo el programa de desarrollo de medicamentos. Por lo tanto, se utilizarán según lo planeado en este estudio, así como dentro de las actividades de investigación relacionadas necesarias para este programa de desarrollo de medicamentos con el fin de:

- comprender cómo funcionan el medicamento del estudio y medicamentos similares en el organismo (es decir, evaluar el modo de acción del medicamento del estudio),
- comprender mejor la enfermedad estudiada y los problemas de salud asociados,
- desarrollar pruebas de diagnóstico para la enfermedad,
- aprender del presente estudio para planificar nuevos estudios o mejorar los métodos de análisis científico,
- publicar los resultados de la investigación en revistas científicas o utilizarlos con fines educativos.

OTRA INFORMACIÓN RELEVANTE

Una descripción de este ensayo clínico estará disponible en **http://reec.aemps.es** según exige la legislación española. Encontrará igualmente información sobre el estudio en **https:// https://clinicaltrials.gov**. Además, transcurrido un año desde la finalización del estudio, estarán disponibles en la base de datos de la Unión Europea el resumen de sus resultados (independientemente de cuáles sean), así como un resumen redactado en un lenguaje comprensible para una persona.

Cualquier nueva información referente a las terapias utilizadas en el estudio y que pueda afectar a su disposición para que su hijo/a participe en el estudio, que se descubra durante su participación, le será comunicada por su médico lo antes posible.

Si la nueva información implica alguna modificación de la hoja de información, se le facilitará la nueva versión del documento, dándosele la oportunidad de decidir si desea que su hijo/a continúe su participación en el estudio.

¿CUÁNDO FINALIZA MI PARTICIPACIÓN EL ENSAYO?

El investigador, el Promotor, el Comité de ética y las autoridades reguladoras que supervisan este ensayo clínico pueden decidir retirar a su hijo/a si consideran que es lo mejor para él/ella.

- Una vez **concluido el periodo de seguimiento** que tendrá una duración de aproximadamente 24 meses, desde la firma del consentimiento.
- **En cualquier momento si usted lo decide**, debiendo comunicarlo al investigador.
- Si el **médico del estudio decidiera suspender la participación de su hijo/a** en el ensayo, por haberse aprobado un nuevo medicamento con mayor eficacia demostrada, por considerar que es lo mejor para su hijo/a, o si usted no siguiese los procedimientos del ensayo clínico, usted recibirá una explicación adecuada del motivo que ha ocasionado la retirada de su hijo/a del estudio.
- Por otras **circunstancias imprevistas,** siempre que el Promotor o las Autoridades Sanitarias lo consideren oportuno.

En todo caso, deberá seguir las indicaciones que le transmita el médico del estudio, para una finalización ordenada del ensayo.

¿QUÉ OCURRIRÁ CON MIS MUESTRAS?

Las muestras de sangre recogidas se asociarán a un código que solo podrá ser relacionado con la identidad de su hijo/a y con su historia clínica por el médico del estudio/colaboradores. Los datos que se deriven de la utilización de estas muestras se tratarán del mismo modo que el resto de datos que se obtengan durante el ensayo. Sus muestras y los datos asociados podrán ser analizados en diversos laboratorios, para los mismos fines del estudio descrito, pero siempre manteniendo la confidencialidad de su identidad de acuerdo a la legislación vigente.

AGRADECIMIENTO:

Sea cual sea su decisión, el promotor y el equipo de investigación quieren agradecer su tiempo y atención.

Junta de Andalucía

Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

Junta de Andalucía
Consejería de Salud y Consumo
Fundación para la Investigación Biosanitaria de Andalucía Oriental – Alejandro Otero

HOJA DE CONSENTIMIENTO DE PARTICIPANTE ANTE TESTIGOS Y/O FAMILIAR/PERSONA VINCULADA DE HECHO

Título: Ensayo clínico Fase I-IIa, unicéntrico, controlado, abierto y aleatorizado, para evaluar la seguridad, factibilidad e indicios de eficacia del uso de un sustituto autólogo de mucosa palatina humana de fibrina-agarosa nanoestructurada generado por ingeniería tisular, en el tratamiento de pacientes con fisura palatina.
Código de protocolo: FIB-BIO-2023-03
Eu CT number: 2023-506913-23-00

Yo,_____
_____<<*nombre y apellidos* ***del padre o tutor legal*** >> como

□ Padre/madre / □ Tutor legal, afirmo que he recibido una explicación satisfactoria sobre el procedimiento del estudio, su finalidad, riesgos, beneficios y alternativas por parte del D/Dª

_____

<<*nombre y apellidos del investigador*>> y que he leído la hoja de información que se me ha entregado sobre el estudio, de modo que:

☐ Ha podido hacer preguntas sobre el estudio

☐ Ha recibido suficiente información sobre el estudio.

☐ Ha hablado con

_____

<<*nombre del investigador*>>

☐ Comprende que su participación es voluntaria.

☐ Comprende que puede retirarse del estudio:

- Cuando quiera,
- Sin tener que dar explicaciones y
- Sin que esto repercuta en los cuidados médicos de mi hijo/a.

El participante acepta que se tomen muestras de su hijo/a para los mismos fines del estudio descrito:

☐SÍ ☐ NO

El padre, madre o tutor legal del participante desea que le comuniquen la información derivada de la investigación que pueda ser relevante para su salud:

☐SÍ ☐ NO

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Presto libremente mi conformidad para que mi hijo/a participe en el estudio.

Firma del representante legal, primer progenitor o persona vinculada de hecho: Fecha: Nombre, firma y fecha de puño y letra por el firmante	Firma del investigador y Nº de colegiado Fecha:

Firma del segundo progenitor (o tutor legal) del menor: <<Nombre y fecha de puño y letra del firmante>>	Fecha: <<fecha de puño y letra del firmante>>

Apéndice 1. Protección de datos de carácter personal relativo al documento Hoja de información al paciente y CI del estudio

Título del estudio	Ensayo clínico Fase I-IIa, unicéntrico, controlado, no enmascarado y aleatorizado, para evaluar la seguridad, factibilidad e indicios de eficacia del uso de un sustituto autólogo de mucosa palatina humana de fibrina-agarosa nanoestructurada generado por ingeniería tisular, en tratamiento de pacientes con fisura palatina.
Código del estudio	FIB-BIO-2023-03
EU CT Number	2023-506913-23-00
Promotor	Fundación para la Investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO)
Investigador Principal	Ricardo Fernández valades
Centro	Hospital Universitario Virgen de las Nieves

De conformidad con lo establecido en el Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos y en la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales, es importante que conozca la siguiente información:

La Fundación para la Investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO) es el promotor de este estudio. Tiene su sede en Granada. Tanto el Centro como el Promotor son responsables de sus respectivos tratamientos, correspondiendo a cada uno de ellos las obligaciones derivadas de su actividad. El centro es el responsable de todos los datos que figuren en la historia y que puedan identificarle y el promotor de los que se recogen en este estudio de forma codificada; es decir, durante su participación en el estudio se le identificará mediante un código y ni el investigador, ni el hospital transferirán al promotor información alguna que pueda identificarle directamente.

La lista que relaciona el código de identificación con los datos que le identifican (nombre, apellido, número de historia clínica…) se guardan de manera confidencial en su centro sanitario.

¿QUÉ OCURRE CON LA CONFIDENCIALIDAD?

El acceso a su información personal identificada quedará restringido al médico del estudio y colaboradores, autoridades sanitarias (Agencia Española de Medicamentos y Productos Sanitarios, autoridades sanitarias extranjeras), al Comité de Ética de la Investigación con medicamentos (CEIm) y personal autorizado por el promotor (monitores del estudio o auditores), cuando lo precisen para comprobar los datos, procedimientos del estudio, y el cumplimiento de normas de buena práctica clínica; pero siempre manteniendo la confidencialidad de los mismos. La identidad de su hijo/a podría ser revelada en casos excepcionales, como situaciones de urgencia médica para su salud o requerimiento legal. El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustarán a lo dispuesto en la normativa aplicable.

Igualmente, en caso de producirse una reacción adversa, los datos identificativos podrán ser comunicados por el Centro a las autoridades sanitarias competentes y a las compañías aseguradoras con las que se hubiese contratado un seguro, a fin de llevar a cabo las gestiones que resulten necesarias.

Los datos codificados pueden ser transmitidos a terceros y a otros países, pero en ningún caso contendrán información que pueda identificar directamente a su hijo/a, como nombre y apellidos, iniciales, dirección, nº de la seguridad social, etc. En el caso de que se produzca esta cesión, será para los mismos fines del estudio descrito o para su uso en publicaciones científicas, pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación vigente.

¿DURANTE CUÁNTO TIEMPO SE GUARDARÁN MIS DATOS?

El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de la salud de su hijo/a.

¿QUÉ DERECHOS TENGO?

Con respecto a los datos, su hijo/a tiene los siguientes derechos que usted podrá ejercer ante el investigador principal y/o centro:

- Puede preguntar en cualquier momento qué datos se están guardando (derecho de acceso), quién los usa y con qué fin; puede solicitar una copia de los datos personales para su propio uso.

- Puede solicitar recibir una copia de los datos personales proporcionados por usted para transmitirlos a otras personas (portabilidad).
- Puede corregir los datos personales de su hijo/a proporcionados por usted y limitar el uso de datos que sean incorrectos (derecho de rectificación y supresión).
- Puede oponerse al uso de los datos personales o restringirlo (derecho de oposición)

Le recordamos que existen algunas limitaciones con objeto de garantizar la validez de la investigación y cumplir con los deberes legales del promotor y los requisitos de autorización de medicamentos. Si decide que su hijo/a deje de participar en el ensayo o retirar su consentimiento sobre el tratamiento de los datos no se podrán eliminar aquellos datos recogidos hasta ese momento. Debe saber que si decide retirar el consentimiento sobre el tratamiento de los datos podría determinar su cese en la participación en el ensayo.

¿CON QUIÉN CONTACTO?

Para ejercitar sus derechos, diríjase al investigador principal del estudio (cuyos datos aparece en la página 8 de la hoja de información superior) o al Delegado/a de Protección de Datos de su Centro, o del promotor.

Delegado de Protección de Datos para todos los centros de la Junta de Andalucía:

Email: dpd.sspa@juntadeandalucia.es

Delegado de Protección de Datos del promotor:

Email: dpd.csalud@juntadeandalucia.es

Así mismo, tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho (a través de su página web *www.aepd.es*).

¿CÓMO SE COMUNICARÁN LOS RESULTADOS?

Una descripción de este ensayo clínico estará disponible en https://reec.aemps.es, según exige la legislación española.

El promotor está obligado a publicar los resultados, tanto positivos como negativos, de los ensayos clínicos autorizados, preferentemente, en revistas científicas antes de ser divulgados al público no sanitario, con independencia de las obligaciones de publicación del informe de los resultados en el Registro Español de estudios clínicos

(REec) y de lo establecido al respecto en el Reglamento (UE) n.º 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014.

Cuando se hagan públicos estudios y trabajos de investigación sobre medicamentos, dirigidos a la comunidad científica, se harán constar los fondos obtenidos por el autor, por o para su realización, y la fuente de financiación.

Se mantendrá en todo momento el anonimato de los sujetos participantes en el ensayo.

SALVAGUARDA PARA LA PROTECCIÓN DE SUS DATOS PERSONALES

Se adoptarán las medidas de protección apropiadas para proteger los datos codificados durante y después del ensayo, entre ellas:

- El acceso a los datos codificados quedará limitado a personas sujetas a obligaciones de confidencialidad (incluida la obligación de no intentar volver a identificar a los pacientes ni descodificar los datos clínicos).
- Los datos codificados se protegerán con medidas de seguridad para evitar su alteración, pérdida y accesos no autorizados y podrán aplicarse medidas adicionales que eviten la identificación.
- Los datos codificados no se compartirán con fines de comercialización directa ni para otros fines que no sean obligaciones legales o que no se consideren investigación científica de conformidad con la legislación vigente en materia de protección de datos. En particular, no se utilizarán para tomar decisiones sobre futuros servicios que se le pudieran ofrecer, como un seguro.

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ANEXO 1. CALENDARIO DE VISITAS Y PROCEDIMIENTOS

Visita	Procedimientos/Evaluaciones
V1 Selección. 4 meses antes de la cirugía.	• Firma del consentimiento informado • Obtención de muestras de sangre, fotografías y Cuestionario de Calidad de Vida.
V2 (Telefónica). 1 mes antes de la cirugía.	• Para confirmar que puede ser incluido en el estudio, y poder asignarle un grupo.
V3 (cirugía)	• Intervención quirúrgica • Revisión por el otorrino, obtención de moldes y fotografías.
V4, 5 y 6 (A las 24, 48 horas, y 7 días de la cirugía	• Revisión de la herida, incluyendo fotografías
V7. A los 14 días de la cirugía	• Revisión de la herida, cuestionario de Calidad de vida y fotografías
V8 y V9. Al mes y medio y 4 meses y medio de la cirugía	• Revisión de la herida y revisión por el otorrino si es necesario.
V10. A los 9 meses de la cirugía	• Revisión, impresiones del paladar y generación de moldes y fotografías. Revisión por el otorrino si es necesario. Cuestionario de Calidad de vida.
V11. A los 15 meses de la cirugía	• Revisión de la herida. Valoración del lenguaje por el logopeda y fotografías
V12. A los 24 meses de la cirugía	• Revisión de la herida. Cuestionario Calidad de vida, fotografías, valoración de la audición por el otorrino si es necesario y del lenguaje por el logopeda.