



BIOITHAS
PROBIOTICS

biotechnology & biomedicine

Vademecum 2023/24

PROBIOTIC BASED PRODUCTS
&
FUNCTIONAL PROBIOTIC STRAINS



Our PROFILE

BIOITHAS is a pharmaceutical company based in Alicante-Spain, set up in 2017.

We are proud to be a globally recognized research center, specialized in the development of precision probiotics with clinical indications, using the human microbiota as a therapeutic target.

We are leader in the enterocutaneous axis, targeting inflammatory skin diseases, but without leaving behind other inflammatory and immunological pathologies.

Today a multidisciplinary team in health sciences works hand in hand at BIOITHAS to develop high quality probiotic products.

Our products have been patented in over fifty countries, approved in over thirty and licensed in over twenty-five.

We strive every day to help people improve their health and quality of life.



BIOITHAS was founded and is led by our **CEO and Scientific Director, Vicente Navarro-López (MD, PhD)**, an over 25 years experienced physician specialist in infectious diseases, and since 2012 devoted to the study of human microbiota and its relationship with disease, especially skin pathologies.



STRAIN SELECTION

Our probiotic strains are selected based on in-house pre-clinical research and other existing studies, and are deposited in the Spanish Type Culture Collection (CECT), among other national collections.



PRODUCTION

Strain cultivation, production and lyophilization is a process we conscientiously control by inspection, test results and certificates of compliance.



CLINICAL TRIALS

We design and perform randomized, double blind, placebo controlled clinical trials to validate the efficacy and the effect of our strains in different pathologies.



PHARMACEUTICAL FORMULATION

We choose the most appropriate nutraceuticals (vitamin and/or minerals) to back up the selected strains and clinical indication in the final pharmaceutical formulation.



PATENT and PUBLICATION

We patent our probiotic formulations and publish our clinical results in indexed scientific journals.



REGULATORY

Our products are registered and approved in Spain and the rest of Europe, and our regulatory affairs team collaborate in the process of registry in your specific country.



PACKAGING and QUALITY CONTROL

We use the state-of-the-art packaging to ensure viability and shelf-life. An exhaustive control of colony-forming unit maintenance is performed with the latest technologies.

Our SCIENTIFIC PRODUCTION

- Navarro-Belmonte MR, et al. *The Effect of an Oral Probiotic Mixture on Clinical Evolution and the Gut and Skin Microbiome in Patients with Alopecia Areata: A Randomized Clinical Trial.* **Cosmetics.** 2024; 11(4):119.
- Eguren C, et al. *A Randomized Clinical Trial to Evaluate the Efficacy of an Oral Probiotic in Acne Vulgaris.* **Acta Derm Venereol.** 2024; 104:adv33206.
- Rodríguez Baeza D, et al. *Cutaneous T-Cell Lymphoma and Microbiota: Etiopathogenesis and Potential New Therapeutic Targets.* **Dermatol Res Pract.** 2024; 2024:9919225.
- Sánchez-Pellicer P, et al. *Rosacea, microbiome and probiotics: the gut-skin axis.* **Front Microbiol.** 2024; 14:1323644.
- Sánchez-Pellicer P, et al. *Bladder Cancer and Probiotics: What Do We Know So Far?* **Cancers (Basel).** 2023; 15(23):5551.
- Picó-Monllor JA, et al. *Influence and Selection of Probiotics on Depressive Disorders in Occupational Health: Scoping Review.* **Nutrients.** 2023; 15(16):3551.
- Feito-Rodríguez M, et al. *Randomised double blind placebo controlled clinical trial to evaluate the effect of a mixture of probiotic strains on symptom severity and the use of corticosteroids in children and adolescents with atopic dermatitis.* **Clin Exp Dermatol.** 2023; 48(5):495-503.
- Galán-Llopis JA, et al. *Role of microbiome in kidney stone disease.* **Curr Opin Urol.** 2023; 33(2):84-89.
- Sánchez-Pellicer P, et al. *How Our Microbiome Influences the Pathogenesis of Alopecia Areata.* **Genes (Basel).** 2022; 13(10):1860.
- Navarro-López V, et al. *Oral intake of Kluyveromyces marxianus B0399 plus Lactobacillus rhamnosus CECT 30579 to mitigate symptoms in COVID-19 patients: A randomized open label clinical trial.* **Med Microecol.** 2022; 14:100061.
- Sánchez-Pellicer P, et al. *Acne, Microbiome, and Probiotics: The Gut–Skin Axis.* **Microorganisms.** 2022; 10(7):1303.
- Maestre-Carballa L, et al. *A Resistome Roadmap: From the Human Body to Pristine Environments.* **Front Microbiol.** 2022; 13:858831.
- Navarro-López V, et al. *Gut Microbiota as a potential predictive biomarker in Relapsing-Remitting Multiple Sclerosis.* **Genes (Basel).** 2022; 13(5):930.
- Sánchez-Pellicer P, et al. *Descriptive Study of Gut Microbiota in Infected and Colonized Subjects by Clostridiodes difficile.* **Microorganisms.** 2021; 9(8):1727.
- Navarro-López V, et al. *Probiotics in the Therapeutic Arsenal of Dermatologists.* **Microorganisms.** 2021; 9(7):1513.
- Alonzo Martínez MC, et al. *Study of the Vaginal Microbiota in Healthy Women of Reproductive Age.* **Microorganisms.** 2021; 9(5):1069.
- Picó-Monllor JA, et al. *Selection of Probiotics in the Prevention of Respiratory Tract Infections and Their Impact on Occupational Health: Scoping Review.* **Nutrients.** 2021; 13(12):4419.
- Climent E, et al. *Changes in Gut Microbiota Correlates with Response to Treatment with Probiotics in Patients with Atopic Dermatitis. A Post Hoc Analysis of a Clinical Trial.* **Microorganisms.** 2021; 9(4):854.
- Navarro-López V, et al. *Efficacy and Safety of Oral Administration of a Mixture of Probiotic Strains in Patients with Psoriasis: A Randomized Controlled Clinical Trial.* **Acta Derm Venereol.** 2019; 99(12):1078-1084.
- Codoñer FM, et al. *Gut microbial composition in patients with psoriasis.* **Sci Rep.** 2018; 8(1):3812.
- Navarro-López V, et al. *Effect of Oral Administration of a Mixture of Probiotic Strains on SCORAD Index and Use of Topical Steroids in Young Patients With Moderate Atopic Dermatitis: A Randomized Clinical Trial.* **JAMA Dermatol.** 2018; 154(1):37-43.
- Ramírez-Boscá A, et al. *Identification of Bacterial DNA in the Peripheral Blood of Patients With Active Psoriasis.* **JAMA Dermatol.** 2015; 151(6):670-1.



Our clinically tested PROBIOTIC BASED PRODUCTS

| | |
|--------------------------------|----|
| ATOPIC DERMATITIS | 7 |
| PSORIASIS | 11 |
| ACNE | 15 |
| ALOPECIA AREATA | 19 |
| DIGESTIVE SYMPTOMS IN COVID-19 | 23 |



Our clinically tested
PROBIOTIC BASED PRODUCTS

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- ✓ Efficacy demonstrated in **two clinical trials**.
- ✓ **Improvement of atopic dermatitis severity** (SCORAD index) in young patients.
- ✓ **Reduction of the use of topical corticosteroids**, avoiding their associated side effects.

TECHNICAL INFORMATION



Strain composition

Bifidobacterium lactis CECT 8145
Bifidobacterium longum CECT 7347
Lactocaseibacillus casei CECT 9104



Daily dose: 1×10^9 cfu/day



Treatment period: ≥ 3 months

*Recommended based
on clinical results*

Product available as:

- **STRAINS BLEND:** $\geq 1 \times 10^{10}$ cfu/g
- **FINISHED FOOD SUPPLEMENT:** sticks, capsules...

*Customized
concentration
and full service
solution available*

Overview and design

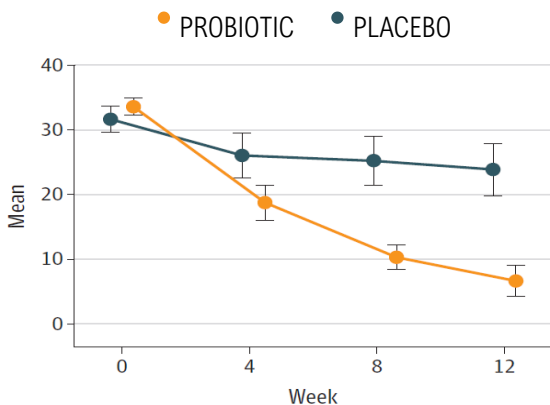
Randomized, double blind and placebo-controlled trial

50 patients (4-17 years) with mild-moderate atopic dermatitis

12-week intervention [Follow-up visits at 0, 4, 8 and 12 week]

1 capsule/day of probiotic (1×10^9 cfu) or placebo

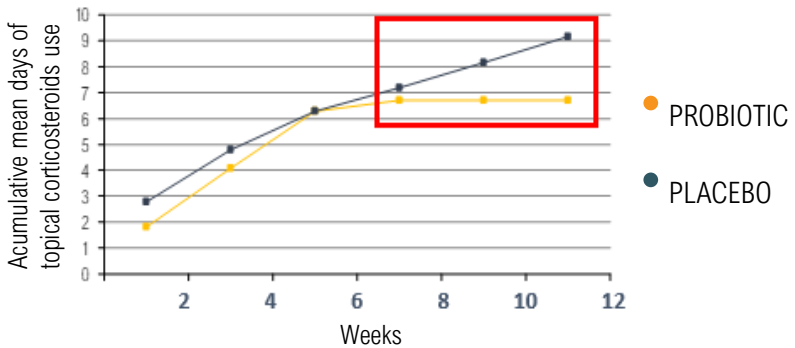
SCORAD index reduction



SCORAD (Scoring of Atopic Dermatitis) index reduction was higher in probiotic versus placebo groups.

At week 12, the severity of atopic dermatitis was reduced in 77.1% in the probiotic group vs 22.7% in the placebo group.

Topical corticosteroids use reduction



Patients in the probiotic group stopped using **topical corticosteroids** in the second part of the study (from week 6), whereas placebo group continued using them.

In practice, we compared the use of topical corticosteroids plus placebo versus the use of probiotics without topical corticosteroids, and the SCORAD index differences between the two groups continued to increase in favor of the probiotic group until the end of the study.

CLINICAL TRIAL 2

Feito-Rodríguez M et al. *Clin Exp Dermatol* (2023)

Same product and clinical trial design, but **higher number of patients** (70)



This second clinical trial **confirmed that the probiotic is effective** in reducing the severity of atopic dermatitis, in addition to promoting less use of topical corticosteroids by patients.

PUBLICATIONS

- **Patent** no. PCT/EP2017/068131
- Clinical trials registration identifier at clinicaltrials.gov:
 - NCT02585986
 - NCT03822624
- Navarro-López V, et al. *Effect of Oral Administration of a Mixture of Probiotic Strains on SCORAD Index and Use of Topical Steroids in Young Patients With Moderate Atopic Dermatitis: A Randomized Clinical Trial.* **JAMA Dermatol.** 2018; 154(1):37-43.
- Climent E, et al. *Changes in Gut Microbiota Correlates with Response to Treatment with Probiotics in Patients with Atopic Dermatitis. A Post Hoc Analysis of a Clinical Trial.* **Microorganisms.** 2021; 9(4):854.
- Navarro-López V, et al. *Probiotics in the Therapeutic Arsenal of Dermatologists.* **Microorganisms.** 2021; 9(7):1513.
- Feito-Rodríguez M, et al. *Randomized double-blind placebo-controlled clinical trial to evaluate the effect of a mixture of probiotic strains on symptom severity and use of corticosteroids in children and adolescents with atopic dermatitis.* **Clin Exp Dermatol.** 2023; 48(5):495-503.

- ✓ Efficacy demonstrated in **clinical trial**.
- ✓ **Improves the severity** of Psoriasis (PASI and PGA indexes).
- ✓ **Reduces the risk of relapse** after the intake of the probiotic.

TECHNICAL INFORMATION



Strain composition

Bifidobacterium lactis CECT 8145
Bifidobacterium longum CECT 7347
Lactiseibacillus rhamnosus CECT 8361



Daily dose: 1×10^9 cfu/day



Treatment period: ≥ 3 months

*Recommended based
on clinical results*

Product available as:

- **STRAINS BLEND:** $\geq 1 \times 10^{10}$ cfu/g
- **FINISHED FOOD SUPPLEMENT:** sticks, capsules...

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Overview and design

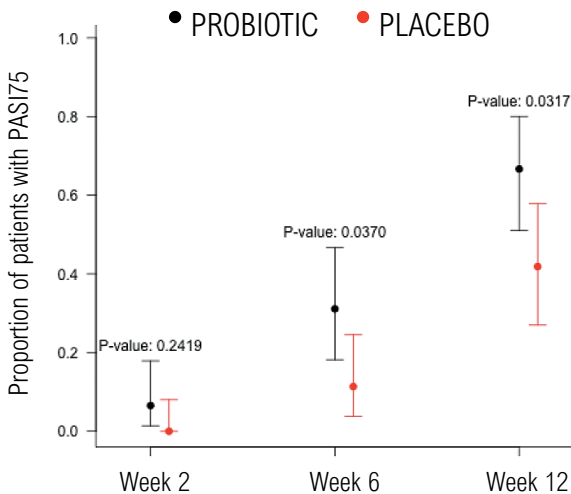
Randomized, double blind and placebo-controlled trial

90 patients with plaque Psoriasis

12-week intervention [Follow-up visits at 0, 2, 6 and 12 week] and 6-months post-intervention follow-up

1 capsule/day of probiotic (1×10^9 cfu) or placebo

PASI reduction of at least 75%

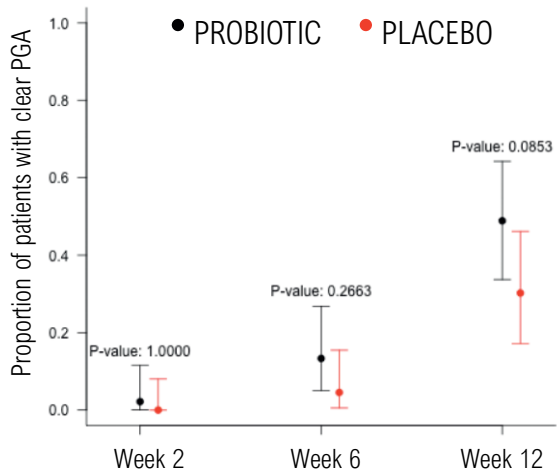


A treatment for psoriasis is considered effective if it reduces PASI (Psoriasis Area and Severity Index) at least 75% (PASI75).

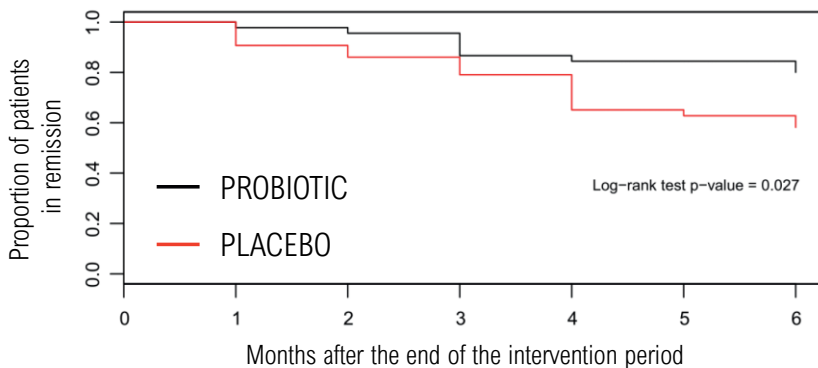
At 12-week follow-up, 66.7% of patients in the probiotic group and 41.9% in the placebo group reach PASI75 ($p < 0.05$).

Physician Global Assessment (PGA)

There were differences in the proportion of patients in the category “clear” of PGA (Physician Global Assessment) between the two groups at week 12: 22 patients (48.9%) in the probiotic group and 13 patients (30.2%) in the placebo group.



Risk of new relapse



A post-intervention follow-up period of 6 months shows that patients previously treated with the probiotic have a **lower risk of relapse** than those who received placebo.

In addition to the efficacy in the severity reduction, the probiotic product has a protective and preventive effect for the appearance of new symptoms.

PUBLICATIONS

- **Patent** no. PCT/EP2017/056719
- Clinical trial registration identifier at clinicaltrials.gov. NCT02576197
- Navarro-López V, et al. *Efficacy and Safety of Oral Administration of a Mixture of Probiotic Strains in Patients with Psoriasis: A Randomized Controlled Clinical Trial.* **Acta Derm Venereol.** 2019; 99(12):1078-1084.
- Ramírez-Boscá A, et al. *Identification of Bacterial DNA in the Peripheral Blood of Patients With Active Psoriasis.* **JAMA Dermatol.** 2015; 151(6):670-1.
- Codoñer FM, et al. *Gut microbial composition in patients with psoriasis.* **Sci Rep.** 2018; 8(1):3812.
- Navarro-López V, et al. *Probiotics in the Therapeutic Arsenal of Dermatologists.* **Microorganisms.** 2021; 9(7):1513.

- ✓ Efficacy demonstrated in **clinical trial**.
- ✓ **Reduction of general severity** of Acne.
- ✓ **Decrease in the number of acne lesions**.

TECHNICAL INFORMATION



Strain composition

Lactocaseibacillus rhamnosus CECT 30031
Spirulina (A. platensis) BEA_IDA_0074B



Daily dose: 1×10^9 cfu/day



Treatment period: ≥ 3 months

*Recommended based
on clinical results*

Product available as:

- **STRAINS BLEND:** $\geq 1 \times 10^{10}$ cfu/g
- **FINISHED FOOD SUPPLEMENT:** sticks, capsules...

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Overview
and
design

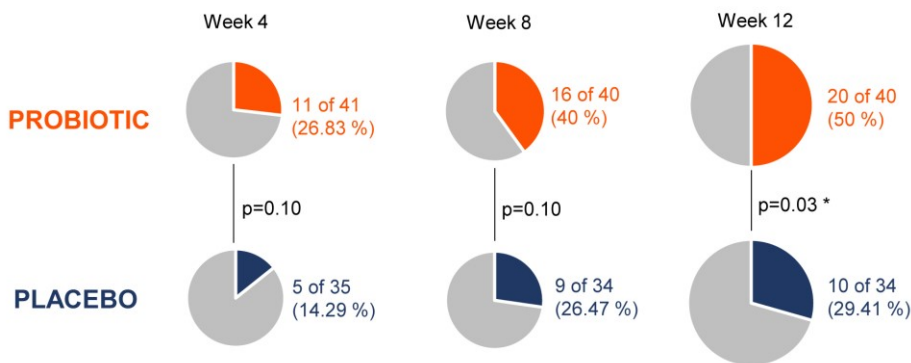
Randomized, double blind and placebo-controlled trial

80 patients (12-30 years) with mild-moderate Acne

12-week intervention [Follow-up visits at 0, 4, 8 and 12 week]

1 capsule/day of probiotic (1×10^9 cfu) or placebo

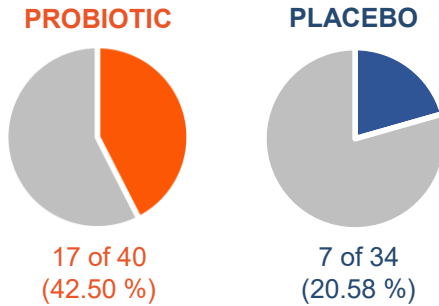
Improvement in AGSS



The main efficacy variable analysis was the number and percentage of cases with response according **AGSS (Acne Global Severity Scale)**.

A greater number of patients with improvement (change of at least one category of less severity) at the end of the study occurs in the probiotic group when compared to the placebo group: 20 of 40 (50.00 %) versus 10 of 34 (29.41 %), respectively.

Patients responding to treatment according to GAGS



The percentage of patients with a clinically significant improvement of at least 30% in the score of **GAGS (Global Acne Grading System)** was significantly higher in probiotic group (42.50 %) compared to placebo group (20.58 %) at the end of the study ($p=0.02$).

Number of acne lesions

The number of total, non-inflammatory and inflammatory acne lesions difference between baseline and 12-weeks follow-up visit were evaluated in both groups.

A significant difference in the reduction of number of non-inflammatory acne lesions was showed in probiotic versus placebo ($p=0.03$). In addition, a reduction that almost reaches statistical significance occurs in total number of lesions ($p=0.06$).

| Lesions type | PLACEBO group | PROBIOTIC group | DIFFERENCE between groups | p |
|-------------------------|-----------------------------|------------------------------|----------------------------|-------------|
| <i>Total</i> | -18.31 [-28.21 to -8.41] | -27.94 [-36.35 to -19.53] | -9.63 [-19.71 to 0.45] | 0.06 |
| <i>Non-inflammatory</i> | -10.54 [-17.43 to -3.66] | -18.60 [-24.38 to -12.82] | -8.06 [-15.37 to -0.74] | 0.03 |
| <i>Inflammatory</i> | -13.87 [-20.26 to -7.48] | -16.41 [-22.47 to -10.35] | -2.54 [-8.47 to 3.40] | 0.40 |

PUBLICATIONS

- **Patent** no. PCT/EP2021/075219
- Clinical trial registration identifier at clinicaltrials.gov. NCT04570319
- Eguren C, et al. *A Randomized Clinical Trial to Evaluate the Efficacy of an Oral Probiotic in Acne Vulgaris*. ***Acta Derm Venereol.* 2024**; 104:adv33206.
- Sánchez-Pellicer P, et al. *Acne, Microbiome, and Probiotics: The Gut-Skin Axis*. ***Microorganisms.* 2022**; 10(7):1303.
- Navarro-López V, et al. *Probiotics in the Therapeutic Arsenal of Dermatologists*. ***Microorganisms.* 2021**; 9(7):1513.

- ✓ Efficacy demonstrated in **clinical trial**.
- ✓ Improvement in the **signs of activity, inactivity and repopulation** of the alopecia.
- ✓ Decrease in the **number of alopecia plaques**.
- ✓ Reduction of the **surface affected** by alopecia areata.

TECHNICAL INFORMATION



Strain composition

Lactocaseibacillus rhamnosus CECT 30580
Bifidobacterium longum CECT 30616



Daily dose: 1×10^9 cfu/day



Treatment period: ≥ 6 months

*Recommended based
on clinical results*

Product available as:

- **STRAINS BLEND:** $\geq 1 \times 10^{10}$ cfu/g
- **FINISHED FOOD SUPPLEMENT:** sticks, capsules...

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Overview and design

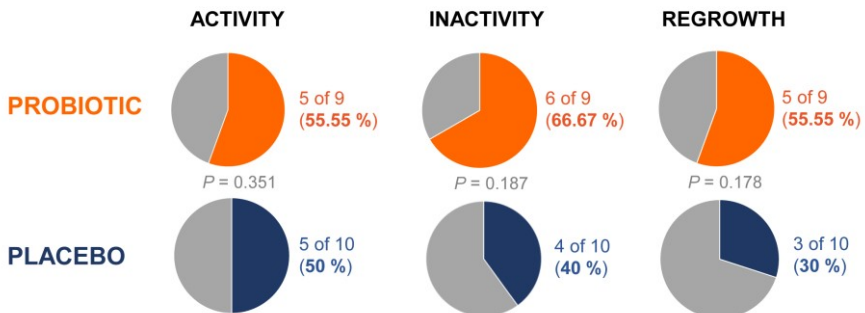
Randomized, double blind and placebo-controlled trial

26 patients with Alopecia Areata

24-week intervention [Follow-up visits at 0, 16 and 24 week]

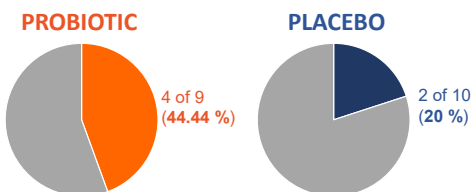
1 capsule/day of probiotic (1×10^9 cfu) or placebo

Clinical signs of alopecia areata



The percentage of patients who improved the clinical signs was higher in the probiotic group compared to placebo: **activity** (55.55% vs. 50%), **inactivity** (66.67% vs. 40%), and **regrowth** (55.55% vs. 30%).

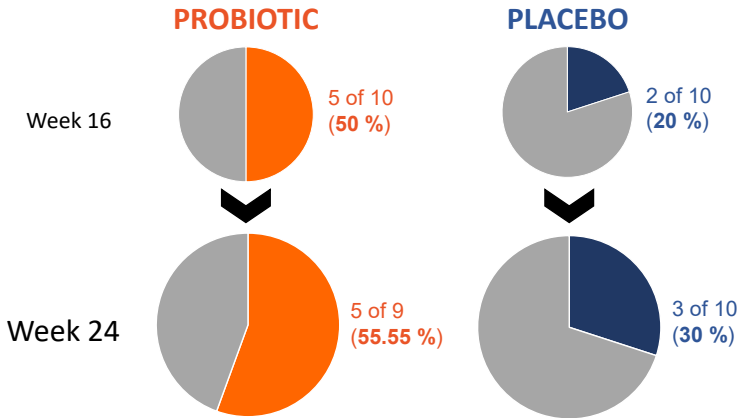
Affected surface area



At week 24, the percentage of patients who reduced the affected scalp surface area according to **SALT (Severity of Alopecia Tool)** scale was higher in probiotic compared to placebo group (44.44% vs. 20%, respectively).

Number of alopecia plaques

The percentage of patients who **reduced the number of alopecia plaques** at the end of the study (24 weeks) was higher in probiotic group (55.55%) compared to placebo (30%).



Two of the eight patients who improved the number of alopecia plaques at the end of the study resolved them completely, belonging both to probiotic group.



PUBLICATIONS

- **Patent** no. PCT/EP2023/063439
- Clinical trial registration identifier at clinicaltrials.gov. NCT05599607
- Navarro-Belmonte MR, et al. *The Effect of an Oral Probiotic Mixture on Clinical Evolution and the Gut and Skin Microbiome in Patients with Alopecia Areata: A Randomized Clinical Trial.* **Cosmetics.** 2024; 11(4):119.
- Sánchez-Pellicer P, et al. *How Our Microbiome Influences the Pathogenesis of Alopecia Areata.* **Genes.** 2022, 13, 1860.
- Navarro-López V, et al. *Probiotics in the Therapeutic Arsenal of Dermatologists.* **Microorganisms.** 2021; 9(7):1513.

- ✓ Efficacy demonstrated in a **clinical trial**.
- ✓ Improvement of the **digestive symptoms associated** to SARS-CoV-2 infection (**COVID-19**).

TECHNICAL INFORMATION



Strain composition

Kluyveromyces marxianus B0399
Lactocaseibacillus rhamnosus CECT 30579



Daily dose: 1×10^9 cfu/day



Treatment period: ≥ 1 month

*Recommended based
on clinical results*

Product available as:

- **STRAINS BLEND:** $\geq 1 \times 10^{10}$ cfu/g
- **FINISHED FOOD SUPPLEMENT:** sticks, capsules...

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Overview
and
design

Open-label, prospective, case-control intervention clinical trial

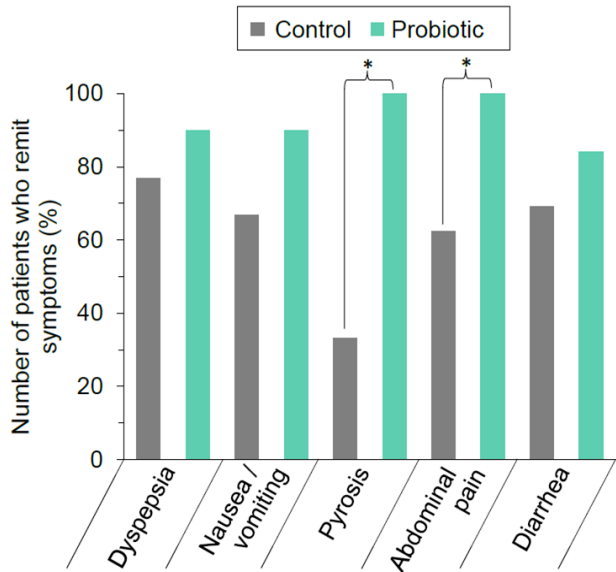
40 patients with active infection of SARS-CoV-2 (COVID-19)

30-days intervention

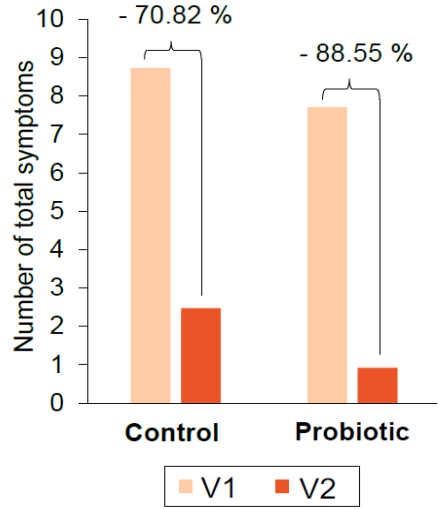
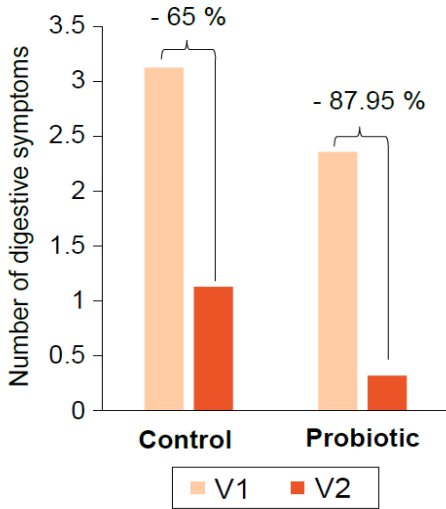
1 capsule/day of probiotic (1×10^9 cfu)

Digestive symptoms

A decrease in the number of patients with digestive symptoms associated with COVID-19 was observed in probiotic compared to control group, with statistically significant differences in the symptoms pyrosis and abdominal pain.



Number of digestive and total symptoms



The decrease in the mean **number of digestive symptoms** associated to the infection was higher in probiotic group than in control group, with statically significant difference.

At the end of the study, it was observed a larger decrease in the mean of the **total number of general symptoms** associated to the infection in the probiotic group, with statically significant difference.

PUBLICATIONS

- Clinical trial registration identifier at clinicaltrials.gov. NCT04390477.
- Navarro-López V, et al. *Oral intake of Kluyveromyces marxianus B0399 plus Lactobacillus rhamnosus CECT 30579 to mitigate symptoms in COVID-19 patients: A randomized open label clinical trial.* **Med Microecol.** 2022; 14:100061.

Our patented functional PROBIOTIC STRAINS

Our **functional probiotic strains** are available as a single strain ingredient or a customized blend to create your unique formulations.

| | Specie | Strain name | Deposit code | Concentration | Clinical indication |
|-----------|---|-----------------|-------------------|-------------------------------|------------------------------------|
| BACTERIA | <i>Lactiseibacillus rhamnosus</i> | AcnePro-Bths | CECT 30031 | $\geq 1 \times 10^{10}$ cfu/g | Acne |
| | <i>Lactiseibacillus rhamnosus</i> | Bths-07 | CECT 30579 | $\geq 1 \times 10^{10}$ cfu/g | Digestive symptoms in COVID-19 |
| | <i>Lactiseibacillus rhamnosus</i> | Bths-08 | CECT 30580 | $\geq 1 \times 10^{10}$ cfu/g | Alopecia Areata |
| | <i>Bifidobacterium longum</i> | Bths-05 | CECT 30615 | $\geq 1 \times 10^{10}$ cfu/g | Inflammatory skin diseases |
| | <i>Bifidobacterium longum</i> | Bths-06 | CECT 30616 | $\geq 1 \times 10^{10}$ cfu/g | Alopecia Areata |
| | <i>Pediococcus acidilactici</i> | Bths-12 | <i>In process</i> | $\geq 1 \times 10^{10}$ cfu/g | Metabolic syndrome and weight loss |
| YEAST | <i>Kluyveromyces marxianus fragilis</i> | Bths-04 | CECT 13203 | $\geq 1 \times 10^8$ cfu/g | Immune system |
| | <i>Kluyveromyces marxianus fragilis</i> | B0399 | B0399 | $\geq 1 \times 10^8$ cfu/g | Digestive symptoms in COVID-19 |
| SPIRULINA | <i>Arthrospira platensis</i> | SPF-Bioithas001 | BEA_IDA_0074B | 3.5-7.5 % phycocyanins | Acne |

CECT: Spanish Type Culture Collection; BEA: Spanish Algae Bank



Clinically tested PROBIOTICS



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