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Comparative phase II clinical trial on the efficacy and tolerability of three dose levels of FR-91 (0.5, 1 and 2 units) versus placebo in the treatment of hip or knee osteo-arthritis during eight weeks : multicentre, double-blind, parallel group, randomized trial in 40 patients.

FINAL REPORT

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SUMMARY

Objective: To compare the efficacy and tolerability of three dose levels of FR-91 (0.5, 1 and 2 Units) (Chacón Farmacéutica) versus placebo in the treatment of mechanical osteo-arthritis of the hip or of the knee after 8 weeks of treatment.

Design: Multi-centre, randomized, double-blind, parallel groups trial.

Study sites: 5 rhumatologists in Belgium:

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Subjects: 41 ambulatory patients suffering from hip (22 patients) or knee (19 patients) osteo-arthritis.

Treatments: According to the randomization list, the patients received i.m. during 8 weeks (o.d. during the first five days and three times per week afterwards), one of the four following treatments: 0.5 U FR-91; 1 U FR-91, 2 U FR-91 or Placebo (Pla).

Main outcome measures: The main parameter of efficacy was the intensity of the pain self-assessed on a 100-mm visual analog scale by the patient at the investigator's practice.

Secondary parameters of efficacy were the algo-functional index of Lequesne, the goniometric measures of the articulation, the intake of paracetamol, the global clinical efficacy assessed on a 4-point rating scale, the weekly self-evaluation of the pain on a 100-mm visual analog scale by the patient at home.

Safety was evaluated on the basis on the general physical examination, laboratory tests, incidence of adverse events, and the general tolerability assessed on a 4-point rating scale.

Statistical methods: Intent-to-treat analysis of efficacy. The intensity of the pain and the algo-functional index were compared between groups using analysis of covariance with the baseline value as covariate and the type of osteo-arthritis as a stratification factor. The global clinical efficacy, the intake of paracetamol, the global tolerability scores were compared between the four groups using the Cochran-Mantel-Haenszel test on standardized ranks adjusted for the type of osteo-arthritis (equivalent to a stratified Kruskal-Wallis rank test). The goniometric measurements were compared for hip and knee osteo-arthritis separately using the Kruskal-Wallis ranks sum test. Weekly VAS were summarized by the minimum and average values during the treatment and during the follow-up period and compared using analysis of variance with stratification for the type of osteo-arthritis.

Results:

Patients disposition:

Inclusion:	41 patients (Pla: 10; 0.5 U: 10; 1 U: 11; 2 U: 10)
Efficacy analysis	40 patients (Pla: 10; 0.5 U: 9; 1 U: 11; 2 U: 10)
Safety analysis	41 patients (Pla: 10; 0.5 U: 10; 1 U: 11; 2 U: 10)

Six patients prematurely stopped the treatment for adverse events (0.5 U: 1; 1 U: 4; 2 U: 1). All of them except one (no.2 in FR-91 0.5 U) have had at least one post-treament evaluation and were included in the efficacy analysis.

Five other patients discontinued the study during the one-month follow-up period (Pla: 1; 1 U: 2; 2 U: 2)

Efficacy :

Adjusted mean changes in pain intensity at the end of treatment are given in the table below.

	Placebo (n=10)	0.5 U (n=9)	1 U (n=11)	2 U (n=10)	p
Adjusted mean (95 % Confidence Interval)	-16.8 (-32.0 ; -1.6)	-12.6 (-28.6 ; +3.3)	-10.2 (-24.9 ; +4.5)	-12.0 (-27.2 ; +3.2)	0.94

The statistical analysis did not show any significant difference between the four treatment groups regarding the evolution (increase or decrease) of the pain intensity at the end of treatment. Analyses carried out after 1, 4 and 8 weeks gave similar results. The four groups yielded similar mean decrease of pain intensity. Moreover, there was a very large inter-individual variability as indicated by wide confidence intervals of mean changes. Although, on average, the pain intensity decreased during treatment, a great variability was observed in the individual profiles.

Secondary parameters of efficacy showed similar results. However the algo-functional index after 4 weeks of treatment seemed to indicate some benefit of FR-91 0.5 U. This index did not show significant difference at the other time-points and in the two other FR-91 dose groups. Goniometric measures of the affected joint did not exhibit relevant improvement in any group. On the basis of the global efficacy after 8 weeks of treatment, approximately 50 % of the patients (18/35) were improved, only one (placebo) exhibited recovery, 10 were status quo and 6 showed deterioration. 75 % of the patients (30/40) took rescue medication during treatment. Although the amount of paracetamol taken seemed higher in the placebo group (median amount : 31.5 vs. 5.5 to 7) the difference was not statistically significant. When all the patients in each group are considered, independently of showing or not improvement, it seems not to be a simple relationship between the amount of paracetamol taken and the decrease of the pain intensity. Examination of patients exhibiting a clinically relevant improvement, defined as a pain intensity decrease of at least 20 mm (VAS), showed that only two patients of the placebo group were such improved and both of them took a large quantity of paracetamol (109 and 149 tablets; mean: 129). In the FR-91 groups, a total of 12 patients (3 to 5 per group) were clinically improved and they took a lower quantity of paracetamol (≤ 25; mean: 7), except one with 148 tablets (mean : 18,8 with this patient). This finding suggests that potential benefit of FR-91 could have been hided by consumption of paracetamol that appeared to act as a confounding factor in this study.

Pese a tomar 6 veces **menos** de calmante, ¡la mitad de los enfermos consumiendo FR-91 (Bio-Bac) mejoraron!. Sólamente uno de los del grupo de placebo mejoraron pese a la dosis mucho más elevada de paracetamol, analgésico comúnmente usado en artrosis.

En cuanto al dolor, sólo dos pacientes del grupo placebo mejoraron ¡tomando 129 tabletas de analgésico!. Por el contrario, 12 (de 30) pacientes mejoraron con FR-91 tomando sólo 7 tabletas de paracetamol. Lo que viene a ser un 35 frente a un 10 por ciento. Porcentajes que dejan claro el beneficio potencial de FR-91 en los pacientes que lo consumieron y que pudieron abandonar prácticamente en su totalidad, la ingesta de paracetamol.

Tolerability :

Approximately 50 % of the patients (21/41) experienced adverse events but none of them was considered serious. However, six patients treated with FR-91 stopped the treatment because of adverse events, mainly local reactions (0.5 U: 1; 1 U: 4; 2 U: 1).

Local reactions at the injection site were more frequent after injection of FR-91 than placebo. Most common symptoms were provoked pain, induration, redness and warmth. Both their intensity and incidence were significantly dose-related.

Systemic adverse events considered as possibly to certainly related to FR-91 were: fever (3 patients), influenza-like symptoms (1), headache (2), dizziness (1), vomiting (1). The overall incidence of adverse events was significantly higher with FR-91 than with placebo.

The global tolerability of FR-91 was judged as good to excellent in most of the patients treated with FR-91; there were however, after 4 or 8 weeks of treatment, 3 cases of poor tolerability and 4 others of mild intolerance, while all the patients but one receiving placebo exhibited an excellent tolerability. The global tolerabilty score was significantly dose-related.

Conclusion :

The results of the present study carried out in 41 patients do not allow to support a statistical evidence of a beneficial effect of FR-91, compared to placebo, in 2-month treatment of osteo-arthritis. However, potential benefit of FR-91 could have been hided by the consumption of paracetamol which seems to act as a confounding factor.

In this perspective, the lowest dose, FR- 91 0.5 unit, seems to be the most beneficial. This possible potential benefit should be manifested in larger controlled studies with a greater number of patients that allow to discern statistically about such confounding factors.

Local reactions were common and related to injected dose FR-91. Systemic events (fever, headache) occurred occasionally.

Sólo los ensayos clínicos en fase III se consideran de relevancia estadística. Éste es de fase II.

Se sugiere que mayor eficacia puede ocultarse tras el uso de paracetamol, usado como calmante.
Ante tales sospechas, se aconseja la realización de estudios con mayor número de pacientes, es decir, ensayos en fase III. El estudio es revelador, y así se reconoce.

La Agencia Española del Medicamento, dependiente del Ministerio de Sanidad, boicotearía la realización de más ensayos clínicos.

Nota:

En Julio de 2003 el Ministerio de Sanidad y Consumo declara que estos ensayos clínicos habían sido falsificados por Chacón Farmacéutica. Estos documentos son los originales, el estudio corresponde al *Biopharma report nº 194.587* y es fotocopia del mismo. De nuevo todos los medios de comunicación recogen en titulares como "Chacón falsificó los ensayos clínicos" las opiniones sesgadas y tendenciosas de la Agencia Española del Medicamento.
A raíz de este estudio, Chacón Farmacéutica publicaría sus propias y valoraciones en la página web www.bio-bac.com, conclusiones que eran subjetivas y que provocaron que Biopharma solicitara a Chacón farmacéutica que matizara esas conclusiones, nunca Biopharma denunciaría a Chacón por falsificar ningún resultado. Los resultados son suficientemente esclarecedores por sí mismos.

Este hecho ha sido utilizado reiteradamente por la Agencia para desacreditar no sólo a Chacón Farmacéutica, sino también la eficacia de Bio-Bac, llegando a afirmar su Director, el Sr. García Alonso que *"este ensayo demuestra que Bio-Bac (el FR-91) es igual de eficaz que el placebo usado"*, como recogemos en un documento de audio en de nuestras páginas. De nuevo, para nuestro asombro, la Agencia Española, la mayor autoridad científica en el ámbito del medicamento, muestra una actitud muy lejos de lo esperable una entidad pretendidamente justa e imparcial y en cuyas manos está la salud de todos los españoles.

Con este documento se demuestra que:

*Jamás Biopharma ha afirmado que Bio-Bac no es eficaz, es más sugiere que sí podría concluirse que lo es, aunque ya se desprenda eficacia de su estudio, pese a no otorgarle relevancia estadíastica, algo normal al tratarse de tan sólo 40 pacientes.
*Biopharma aconseja y ve factible la realización de ensayos clínicos avanzados para poder aseverar la eficacia del producto de manera estadística. Está lejos de descartar tal eficacia.
*Que la Agencia Española conoce este estudio y que no da ningún valor. Que lejos de analizar sus evidencias y fomentar la investigación, trata de ocultar sus conclusiones y echarlos por tierra mediante medias verdades que son grandes mentiras.
*Que la Agencia, primero no permite la realización de ensayos en España y luego interpreta de manera curiosísima los efectuados en importantes laboratorios europeos, llegando a afirmar lo contrario de lo que en ellos se constata.

Muchas personas, entre ellos miembros de la asociación, han observado cómo Bio-Bac es un producto enormemente beneficioso para el tratamiento de la artritis. Existen casos de niños con evoluciones impresionantes.
A ninguno de ellos les extraña las conclusiones de este estudio, a nadie sorprende que Bio-Bac sea eficaz estas patologías. Este estudio no hace más que confirmar formalmente lo que ya sabíamos.

Poco después Chacón Farmacéutica realizó ensayos clínicos en fase III en Tiblisi, Georgia, mostrando, ya, definitivamente la eficacia de Bio-Bac en Artritis. A estos estudios jamás se ha referido, sin embargo, la Agencia Española del Medicamento.