Summary of results:

Participant disposition: A total of 62 patients were screened, and 51 of them were randomised in France (N=28, 54.9%) and Italy (N=23, 45.1%). Fourteen (14) patients discontinued the study, of whom 7 died, and 37 patients completed the study.

Demography and baseline characteristics: Patient demographics and baseline characteristics were similar between the 2 treatment groups In both groups, most patients were male (52.9% in the IFB-088 group, and 64.7% in the placebo group), but the placebo group had more female (11,8%) which is of importance as the study has a 2:1 randomization. The mean age was 62.4 (SD: 9.6) years in the IFB-088 group, and 61.1 (SD: 11.0) years in the placebo group. No patient currently smoked tobacco in the placebo group, however 11.8% of patients in the IFB-088 group reported currently smoking (mean of 6.8 [SD: 2.6] cigarettes per day). In both treatment groups, 88.2% of patients had sporadic ALS. The mean time from the first ALS symptoms onset to screening was quite similar in both groups (11.51 [SD: 3.80] and 12.34 (SD: 4.01) months in placebo and IFB-088 arms, respectively), and so was the mean time from ALS diagnosis to screening (3.67 [SD: 2.77] and 4.11 [SD: 2.93] months, respectively). Progression rate at screening was however lower in the placebo arm in comparison with IFB-088 arm: 0.44 (SD: 0.29) and 0.53 (SD: 0.23) point/month, respectively, and ALSFRS-R scores were lower in the IFB-088 arm (42.2 [SD: 2.7] compared with (43.9 [SD: 2.1] in the placebo arm). These differences suggest that patients included in the experimental arm were more severely affected on average than those included in the placebo arm. Overall, 78.4% of patients had at least one medical history. The most common medical history was Psychiatric disorders (33.3%), most frequently depression (19.6%), similar in both treatment groups.

Safety: The overall incidence of TEAEs was 73.5 and 58.8 % in IFB-088 and placebo arms respectively. Most TEAEs were grade 1 (55.9% in the IFB-088 group versus 41.2% in the placebo group). In both treatment groups, 23.5% of patients reported at least one serious TEAE. In the IFB-088 arm, 5.9% of patients had a serious TEAE considered related to the study drug. Additionally, 14.7% and 11.8% of patients in the IFB-088 and placebo groups respectively died during participation in the study. TEAEs leading to definitive study drug discontinuation occurred in 8.8% of patients in the IFB-088 group. There was no need to adjust the dose, and no patients at increased risk were identified.

No drug-induced crystals were detected in the 89 urine samples from participants in the P288ALS trial using conventional urine crystal characterisation techniques.This finding confirms the hypothesis that crystals found in rats' kidneys in preclinical studies were a species-specific adverse event.

Overall, the favourable safety profile of IFB-088, observed in the phase 1 trial in healthy volunteers was confirmed in this study. Mild gastrointestinal AEs were more frequent than in the placebo arm, but no patient discontinued treatment for toxicity reasons.

Efficacy: In the FAS, using Estimand 1 for imputation of missing data, the adjusted mean change of the ALSFRS-R score from baseline to 6 months was -11.21 (SE: 1.93) (95% CI: -15.08; -7.34) in the IFB-088 group, and -10.87 (SE: 2.77) (95% CI: -16.45; -5.30) in the placebo group. The difference between treatment groups was not statistically significant (LS mean difference: -0.33 [SE: 3.45], 95% CI: -7.27; 6.60, p=0.923). Results obtained using Estimands 2 and 3 were of the same type. In the PPS: the adjusted mean change of the ALSFRS-R score from baseline to 6 months was -6.02 (SE: 0.96) (95% CI: -7.97; -4.07) in the IFB-088 group, and -8.03 (SE: 1.19) (95% CI: -10.44; -5.62) in the placebo group. The difference between treatment groups was close to statistical significance (adjusted mean difference: 2.00 [SE: 1.57], 95% CI: -1.17; 5.18, p=0.209).

Since imbalance between groups at baseline was shown, suggesting a more severe population in the IFB-088 arm, and NfL turned out to be an important prognostic factor, a *post hoc* analysis was performed with adjustment on baseline NfL on top of baseline ALSFRS-R and treatment. This *post hoc* analysis of the change from baseline in ALSFRS-R total score at 6 months showed a treatment effect of +1.5 points favoring the IFB-088 group in the FAS. When excluding patients who died before 6 months, the treatment effect increased to +3.3 points (p=0.24) in the FAS. A similar effect was seen in the PPS, with a treatment effect of +2.5 points (p=0.11) which is considered as statistically significant.

In the FAS (based on estimand 1), the bulbar subscore decline was more pronounced in the IFB-088 group than in placebo group (LS mean difference: -1.23, p=0.115), with *post hoc* analysis confirming a lower decline in the placebo arm across all populations, though not statistically significant. For the motor subscore, no significant difference was observed between groups (LS mean difference: -1.25, p=0.526), and *post hoc* analyses showed similar declines in both arms. For the respiratory subscore, while the overall difference was not statistically significant (LS mean difference: 0.94, p=0.410), *post hoc* analyses showed a consistently lower

decline in the IFB-088 group, reaching statistical significance in the FAS without deaths (p=0.001) and per protocol populations (p=0.005).

The *post hoc* analyses of ALSFRS-R subscores indicated that the overall treatment effect was primarily driven by the respiratory subscore. Excluding patients who died, the respiratory subscore showed a treatment effect of +2.4 points (p=0.001) in the FAS and +2.2 points (p=0.005) in the PP set.

In the FAS, the mean ALS-MITOS score was 0.1 (SD: 0.2) in the IFB-088 group and 0.0 (SD: 0.0) in the placebo group at baseline. The difference in proportions of non-progressors at 6 months was not statistically significant between treatment groups in the FAS according to Estimand 1 (58.8 % in the IFB-088 arm and 70.6 % in the placbo arm, Estimate: -0.118, p=0.398). Similarly, in the PPS, the difference in proportions of non-progressors at 6 months was not statistically significant between treatment groups (83.3 % in the IFB-088 arm and 75.0% in the placbo arm, Estimate: 0.083, p=0.529).

In the FAS, the mean King's College score was 2.1 (SD: 0.8) in the IFB-088 group and 1.6 (SD: 0.8) in the placebo group at baseline, and gradually increased over time from baseline to 6 months in both treatment groups. The difference in proportions of non-progressors according to Estimand 1 was not statistically significant between treatment groups (32.4 in the IFB-088 arm and 35.3 in the placebo arm, Estimate: -0.029, p=0.835). In the PPS, the mean King's College score was 2.2 (SD: 0.8) in the IFB-088 group and 1.6 (SD: 0.8) in the placebo group at baseline, and gradually increased over time from baseline to 6 months in both treatment groups. The difference in proportions of non-progressors was not statistically significant between treatment groups (Estimate: 0.083, p=0.598)

The decrease in SVC was milder in the IFB-088 group compared to placebo; however, the difference was not statistically significant. Blood gas levels remained stable overall.

Bioimpedance data are not interpretable due to the low number of patients with data available at all time points, ranging from 13 to 14 patients. Quality of life declined during the study in both groups, with an impairment of the same order of magnitude.

As regards to biomarkers, the data quality of several biomarkers was not sufficient to perform data analyses, due to either (i) missing data, or (ii) biomarker levels below or above limits of quantification (BLQ, ALQ). Therefore, the analyzed biomarkers are limited to: (i) neurodegeneration biomarkers: NfL, NfH, P75ecd/creatinine, (ii) oxidative stress biomarkers: 8-oxodG/creatinine, (iii) (neuro)inflammation biomarkers: TGFbeta1, neopterin/creatinine, BDNF, FGF21, GDF15, MCP1, VEGF.

In FAS at 6 months, plasmatic NfL concentrations increased by 17% in both the IFB-088 and placebo groups. The adjusted mean ratio between treatment arms was 1.04 (95% CI: 0.89–1.21, p=0.609), indicating no statistically significant difference between groups. In PP analysis, the percentage change in NfL plasmatic concentration from baseline to 6 months showed an increase of +19.5% in the IFB-088 group, and +23.8% in the placebo group. The difference between treatment groups was not statistically significant.

In PP, the percentage change in NfH plasmatic concentration from baseline to 6 months showed an increase of +9.6% in the IFB-088 group, and +20.2% in the placebo group. The difference between treatment groups was not statistically significant.

In PP, the percentage change in p75ecd concentration in urine from baseline to 6 months showed an increase of +24.3% in the IFB-088 group, and +67.3% in the placebo group. The difference between treatment groups was statistically significant (p=0.0243 placebo 6 month (V4) vs IFB-088 6 month (V4) - 2-way ANOVA followed by uncorrected Fisher's LSD).

In PP, the percentage change of concentration of oxidative stress biomarker 8-OHdG in urine from baseline to 6 months showed an increase of +18.5% in the IFB-088 group, and +60.1% in the placebo group, this difference between treatment groups being not statistically significant.

In PP, the percentage change in TGF-beta1 plasmatic concentration from baseline to 6 months showed a decrease of -11.9% in the IFB-088 group, and an increase of +52.5% in the placebo group. The difference between treatment groups was statistically significant (p=0.0009 placebo 6 month (V4) vs IFB-088 6 month - 2-way ANOVA followed by uncorrected Fisher's LSD).

In PP, the percentage change in neopterin concentration in urine from baseline to 6 months showed an increase of +11.8% in the IFB-088 group, and +79% in the placebo group. The difference between treatment groups was statistically significant (p=0.0045 placebo 6 month (V4) vs IFB-088 6 month (V4) - 2-way ANOVA followed by uncorrected Fisher's LSD).

Name of sponsor/Company: InFlectis BioScience	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of finished product: Not applicable		
Name of active ingredient: IFB-088		

In PP, the percentage change in BDNF plasmatic concentration from baseline to 6 months showed an increase of +13.6% in the IFB-088 group, and +48.6% in the placebo group. The difference between treatment groups was not statistically significant.

In PP, the percentage change in FGF-21 plasmatic concentration from baseline to 6 months showed an increase of +19.2% in the IFB-088 group, and +60.2% in the placebo group. The difference between treatment groups was not statistically significant.

In PP, the percentage change in GDF15 plasmatic concentration from baseline to 6 months showed an increase of +14.5% in the IFB-088 group, and +9.6% in the placebo group. The difference between treatment groups was not statistically significant.

In PP, the percentage change in MCP-1 plasmatic concentration from baseline to 6 months showed an increase of +12.8% in the IFB-088 group, and a decrease of -11.4% in the placebo group. The difference between treatment groups was statistically significant (p=0.0346 placebo 6 month vs IFB-088 6 month - 2-way ANOVA followed by uncorrected Fisher's LSD).

In PP, the percentage change in VEGF-alpha plasmatic concentration from baseline to 6 months showed an increase of +5.2% in the IFB-088 group, and +26.3% in the placebo group. The difference between treatment groups was not statistically significant

In a *post hoc* analysis, additional biomarkers have been assessed by mass-spectrometry in plasma extracellular vesicles of patients from the PP: TDP-43, PRDX-6, Bip, DNAJC7.

Post hoc analysis of the percentage change in TDP-43 concentration in plasma extracellular vesicles, from baseline to 6 months showed a decrease of -7.3% in the IFB-088 group, and an increase of +20.5% in the placebo group. The difference between treatment groups was statistically significant (p=0.03 placebo 6 month vs IFB-088 6 month - 2-way ANOVA followed by uncorrected Fisher's LSD).

In a *post hoc analysis*, the percentage change in PRDX-6 concentration in plasma extracellular vesicles from baseline to 6 months showed a slight increase of +4 % in the IFB-088 group, and an increase of +75.3% in the placebo group. The difference between treatment groups was statistically significant (p=0.04 placebo 6 month vs IFB-088 6 month - 2-way ANOVA followed by uncorrected Fisher's LSD).

Post hoc analysis of the percentage change in Bip and DnaJC7 concentration in plasma extracellular vesicles from baseline to 6 months showed an increase of +17.8% in the IFB-088 group, and an increase of +33.4% in the placebo group for Bip and a decrease of -11.5% in the IFB-088 group, and an increase of +14.9% in the placebo group for DnaJC7. The difference between treatment groups was not statistically significant for Bip. For DnaJC7, the difference between treatment groups was statistically significant (p=0.006 placebo 6 month vs IFB-088 6 month - 2-way ANOVA followed by uncorrected Fisher's LSD).

In the FAS, the mean change in ALSAQ-40 at 6 months was 25.4 (SD: 23.0) in the IFB-088 group, and 21.2 (SD: 19.3) in the placebo group.

Pharmacokinetic/Pharmacodynamic: Non-compartmental analysis and population pharmacokinetic (popPK) modeling revealed significant interindividual variability in the exposure to IFB-088 and IFB-139. The estimated pharmacokinetic parameters, particularly the high coefficient of variation for AUC and Cmax, highlight the heterogeneity in the distribution and elimination of these compounds among the studied subjects.

The popPK analysis provided a more detailed characterization of this variability by describing both molecules using a two-compartment model with first-order absorption and elimination. Marked interindividual variability was observed, partly attributable to the extensive metabolism of IFB-088 by cytochrome P450 CYP1A2 (involved in 73% of IFB-088 metabolism), but also by cytochrome P450 CYP2C19 (responsible for 11% of IFB-088 metabolism) and CYP2D6 (responsible for 17% of IFB-088 metabolism).

These observations suggest that drug interactions may contribute to the observed variability in exposure. Integrating these findings into future phases of clinical development could help optimize dosing regimens and better control exposure variability, thereby improving both treatment efficacy and tolerability.

Name of sponsor/Company: InFlectis BioScience	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of finished product: Not applicable	**Volume:** **Page:**	
Name of active ingredient: IFB-088		

Conclusion: The safety evaluation of IFB-088 indicates that the treatment is generally well-tolerated, with a similar overall incidence of serious TEAEs compared to placebo. While the IFB-088 group had a slightly higher proportion of drug-related serious TEAEs and fatal TEAEs, these events were limited to a small subset of patients (5.9%), and the majority of adverse events were mild in severity . Treatment discontinuations were not generally due to toxicity but to disease progression.

No population at increased risk of toxicity was identified, reinforcing IFB-088's acceptable safety profile within the studied dosing regimen. The absence of drug-induced crystals in urine samples, as confirmed by crystalluria and FTIR analyses, provides additional reassurance regarding the renal safety of IFB-088 metabolites.

Given these findings, IFB-088 appears to be a generally safe and tolerable treatment option for ALS patients. However, the occurrence of 2 sudden deaths in the IFB-088 arm underscores the need for careful patient monitoring in future studies. Further research with larger patient populations and longer follow-up periods is warranted to better characterize the safety profile and to ensure that any risks associated with IFB-088 can be effectively managed.

The efficacy evaluation suggests that IFB-088 did not significantly slow ALS progression compared to placebo in the overall study population over 6 months, as measured by ALSFRS-R score. However, the study was not designed to show efficacy and an imbalance was shown between the 2 arms, with a likely more severe population included in the IFB-088 arm. Since NfL was shown to be a prognostic marker, post hoc analyses adjusted on this parameter were performed and indicated a potential benefit of IFB-088 in patients who survived beyond 6 months, with a notable improvement in respiratory function, a critical determinant of ALS progression and patient quality of life.

Biomarker analyses provide strong support for IFB-088's first-in-class mechanism of action. This molecule addresses major ALS pathogenic mechanisms, including TDP-43 mislocalization, oxidative stress, neurodegeneration, and inflammation.

PK variability, driven by extensive metabolism via cytochrome P450 enzymes, suggests that individual patient factors and potential drug interactions could influence treatment response, indicating the importance of refining dosing strategies in future studies.

A significant pharmacokinetic/pharmacodynamic (PK/PD) relationship was observed between plasma IFB-088 exposure and ALS biomarkers, such as TDP-43 and BiP in plasma exosomes, as well as 8-OHDG in urine. The identification of IFB-088 PD biomarkers will inform the design of future clinical trials.

Future clinical trials should consider larger sample sizes and stratified randomization to avoid imbalances between arms, as well as longer treatment durations to provide more safety data and allow adequately powered efficacy analyses. Special attention should be given to respiratory function, a key driver of ALS prognosis. Additionally, optimizing IFB-088's dosing regimen to manage PK variability could enhance both efficacy and tolerability, potentially improving outcomes for ALS patients.

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