TRIALS study: double-blind, placebo-controlled, exploratory RCT to assess safety and efficacy of IFB-088 in patients with bulbar-onset ALS

InFlectis BioScience

S. Attarian[1], E. Bernard[2], C. Boutoleau-Bretonnière[3], J. Mandrioli[4], P. Corcia[5], E. Dalla Bella[6], M. Filosto[7], S. Morino[8], P. Cintas[9], I. Di Meo[10], V. Tiranti[10], V. Leoni[11,12], A. Di Palma[13], D. Perico[13], P. Mauri[13], P. Scalmani[14], M. Vizziello[6], M. Cattaneo[6], E. Giagnorio[15], E. Salvi[6], 16, S. Marcuzzo[15, 17], P.Guédat[18], P. Miniou[18], E. Abgueguen[18], B. Lejeune[18], A. Visbecq[18], G. Lauria[6, 19].

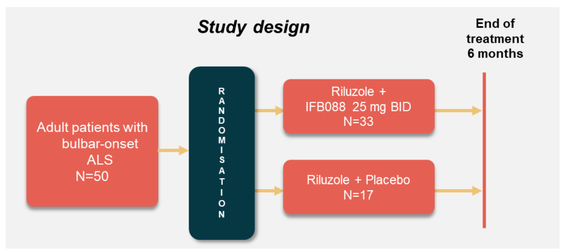
1- CHU Timone Service de Neurologie - Maladies neuromusculaires et SLA, 264 rue St Pierre, 13005 Marseille, France
2- Hôpital Pierre Wertheimer Service de neurologie - troubles du mouvement et pathologies neuromusculaires, 59 boulevard Pinel, 69677 Bron, France
3- CHU de Nantes – Hôpital Laennec Neurologie, Bd du Professeur J. Monod, 44093 Nantes, France
4- Dipartimento Di Scienze Biomediche Metaboliche E Neuroscienze, Universita' Di Modena E Reggio Emilia, VIA P. GIARDINI 1355, 41126 Modena, Italy
5- CHU Bretonneau, CRMR SLA, 2 boulevard Tonnelle, 37044 Tours, France
6- ALS Centre, 3rd Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
7- Centro Clinico NeMO-Brescia per le Malattie Neuromuscolari di Brescia Dipartimento di Scienze Cliniche e Sperimentali, Università degli Studi di Brescia, Paolo Richiedei 16, 25064 Gussago, Italy
8- UOC Neurologia, AOU Sant'Andrea, Via di Grottarossa 1035-9, 189 Roma, Italy
9- Service de Neurologie et d'explorations fonctionnelles, Centre Hospitalier Universitaire de Toulouse, 31000 Toulouse, France
10- Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
11- Laboratory of Clinical Pathology and Toxicology, Hospital Pio Xi of Desio, Italy
12- Department of Medicine and Surgey, University of Milano-Biccoca, Monza Italy
13- Institute for Bimedical Technologies, National Research Council (ITB-CNR), Segrate, Milan, Italy
14- Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
15- Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
16- Computational Multi-Omics of Neurological Disorders (MIND) Lab, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
17- Brain-targeted Nanotechnologies (BraiNs) Lab, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
18- InFlectis BioScience SAS, 21 rue La noue Bras de Fer, 44200 Nantes, France
19- Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy

Background

- Pathophysiology of amyotrophic lateral sclerosis (ALS) is complex, including, among other abnormalities, TDP-43 mislocalization, oxidative stress, endoplasmic reticulum stress and activation of unfolded protein response signaling pathways.
- IFB-088, a multifunctional molecule targeting major cellular mechanisms implicated in ALS, has shown to be efficacious to reduce protein burden and its consequences *in vitro* and in animal ALS models. A phase 1 study in healthy volunteers showed a favorable safety profile.
- Guanabenz, which is very close to IFB-088 (chemical structure and pharmacological effects) showed statistically significant benefits in a randomized double-blind phase 2 study, especially in patients with bulbar-onset ALS (Dalla Bella E et al. Brain 2021).

Methods

- Randomized (2:1), double-blind, placebo-controlled, parallel-group, phase 2 exploratory study (NCT05508074)



- Treatment during 6 months + 1 month follow-up
- Primary objective: To assess the safety and tolerability of IFB-088
- Secondary objectives:
  - To show signals of efficacy, using ALSFRS-R, ALS-MITOS, King's College score, respiratory function (Slow Vital Capacity and arterial blood gases)
  - To investigate QoL (ALSAQ-40)
  - To determine PK parameters, establish a PK population model, and perform PK/PD analyses (blood sampling at the M1 visit)
  - To investigate the effect of IFB-088 on biomarkers (neurodegeneration, inflammation and oxidative stress)
- Descriptive statistics were used for safety parameters
- Efficacy was analyzed by descriptive statistics and comparison of IFB-088 and placebo arms, with a 2-sided α risk of 0.2.
- Change in ALSFRS-R score from baseline to M6 was analyzed using an analysis of covariance model including treatment (IFB-088 vs placebo), and baseline ALSFRS-R score as continuous covariates. Due to the imbalance between arms, a *post hoc* analysis of the change in the ALSFR-S total score and subscores (bulbar, motor, and respiratory) was performed at M6 using the same model adjusted on baseline neurofilament (NfL) on top of treatment and baseline ALSFR-S.
- Changes in ALS-MITOS and King's College scores compared the proportion of progressors between both arms.
- Analyses were performed in the FAS population, with missing data replaced using an Estimand defined as follows
  - Missing data due to deaths from disease progression: ALSFRS-R score at M6 was imputed by the worst value (i.e. 0)
  - Other reason (including death not related to disease progression):
    - if ALSFRS-R score available at M3, ALSFRS-R score at M6 was imputed by linear extrapolation given baseline and M3 values.
    - if ALSFRS-R score missing at M3, ALSFRS-R score at M6 was imputed by linear extrapolation based on the predicted value in the linear regression model within the treatment group to which patient was randomized
- Supportive analyses were performed in the PP population

Results

Patients

61 patients were screened, 51 were randomized (28 in France and 23 in Italy) and 37 completed the study. Reasons for the 14 premature discontinuations were death while on study (n=7), consent withdrawal (n=3), patient wrongly randomized (n=1), poor compliance (n=1), ICU hospitalization (n=1), worsening of clinical condition (n=1). In total, 41 patients had data available at 6 months, and the Per Protocol (PP) population comprised 40 patients.
All patients were Caucasians. Main baseline characteristics are shown on Table 1. They were well balanced between the 2 arms except for the sex ratio with a higher proportion of men in the placebo arm, and for the ALS severity, slightly more pronounced in the IFB-088 arm (higher mean and median progression rates, lower mean and median ALSFRS-R scores, higher NfL levels).

	IFB-088, n=34	Placebo, n=17	Total, n=51
Sex, n (%)			
Males	18 (52.9)	11 (64.7)	29 (56.9)
Females	16 (47.1)	6 (35.3)	22 (43.1)
Age (years)			
Mean ± SD	62.4 ± 9.6	61.1 ± 11.0	62.0 ± 10.0
Median (range)	64 (35-80)	63 (40-75)	64 (35-80)
BMI at screening (kg/m²)			
Mean ± SD	24.5 ± 3.6	23.9 ± 4.1	24.3 ± 3.8
Median (range)	24.6 (18.0-33.1)	22.5 (19.4-33.1)	23.6 (18.0-33.1)
Time from 1st symptoms to screening (months)			
Mean ± SD	12.3 ± 4.0	11.5 ± 3.8	12.1 ± 3.9
Median (range)	12.3 (5.0-18.3)	11.3 (5.8-17.2)	12.0 (5.0-18.3)
Time from diagnosis to screening (months)			
Mean ± SD	4.1 ± 2.9	3.7 ± 2.8	3.9 ± 2.9
Median (range)	3.2 (1.1-12.5)	2.6 (1.1-10.2)	3.0 (1.1-12.5)
Progression rate at screening (point/month)			
Mean ± SD	0.53 ± 0.23	0.44 ± 0.29	0.5 ± 0.25
Median (range)	0.5 (0.2-1.2)	0.3 (0.2-1.2)	0.4 (0.2-1.2)
Type of ALS, n			
Sporadic	30	15	45
Familial	2	1	3
Unknown	2	1	3
ALSFRS score at baseline			
Mean ± SD	42.2 ± 2.7	43.9 ± 2.1	42.7 ±2.6
Median (range)	43 (37-46)	45 (38-46)	44 (37-46)
Neurofilament, pg/mL, mean ± SD	94.5 (42.3)	73.4 (38.2)	

Table 1: Baseline characteristics

Efficacy

- In the primary analysis, the comparison of ALSFRS-R scores did not show statistically significant differences in the FAS population. In the PP population (n=40), IFB-088 behaved better than placebo, with a p-value close to the predefined significance level (p=0.209 vs 0.200) (Table 3).

Primary analysis*, FAS population	IFB-088, n=34	Placebo, n=17
Adjusted mean (SE)	-11.21 (1.93)	-10.87 (2.77)
95% CI	-15.08; -7.34	-16.45; -5.30
Adjusted mean difference (SE)	-0.33 (3.45)	
95% CI	-7.27; 6.60	
p-value	0.923	
Primary analysis*, per protocol population	**IFB-088, n=24**	**Placebo, n=16**
Adjusted mean (SE)	-6.02 (0.96)	-8.03 (1.19)
95% CI	-7.97; -4.07	-10.44; -5.62
Adjusted mean difference (SE)	2.00 (1.57)	
95% CI	-1.17; 5.18	
p-value	0.209	

Table 3: Estimated mean difference on the change of the ALSFRS-R score from V0 to 6 months – Primary analysis *Adjustment on treatment and baseline ALSFRS-R score

- The observed imbalance between treatment groups at baseline suggested that patients in the IFB-088 arm entered the study in a more severe condition. A *post hoc* analysis was performed to compensate for this imbalance by adjusting on NfL on top of ALSFRs-R and treatment. It showed a lower decline in IFB-088 arm in the FAS and PP populations. The clinically meaningful slowing of ALSFRS-R decline reached the pre-specified 2-sided level of significance of 0.20 (p=0.11) in the PP population (Table 4).

Post hoc analysis **	IFB-088	Placebo
FAS population		
Adjusted mean (SE)	-10.6 (1.8), n=34	-12.1 (2.7), n=17
Adjusted mean difference (SE), [95%CI)	1.5 (3.3) [-5.1 ; 8.2]	
p-value	0.65	
FAS without deaths		
Adjusted mean (SE)	-7.7 (1.6), n=29	-10.9 (2.1), n=17
Adjusted mean difference (SE), [95%CI)	3.3 (2.8), [-2.3 ; 8.8]	
p-value	0.24	
Per Protocol population		
Adjusted mean (SE)	-5.8 (0.9), n=24	-8.4 (1.2), n=16
Adjusted mean difference (SE), [95%CI)	2.5 (1.6), [-0.6 ; 5.7]	
p-value	0.11	

Table 4: Estimated mean difference on the change of the ALSFRS-R score from V0 to 6 months – Post hoc analysis **Adjustment on treatment, baseline ALSFRS-R score and NfL baseline

- ALSFRS-R subscores (bulbar = sum of items 1 to 3, motor = sum of items 4 to 9, respiratory = sum of items 10 to 12) suggested a positive effect of IFB-088 on respiratory items (Table 5)

	IFB-088, n=34	Placebo, n=17	P-value
Bulbar Subscore			
Primary analysis – Adjusted mean decline (SD)	-3.92 (0.44)	-2.69 (0.62)	0.115
Post hoc analysis – Adjusted mean decline (SD)	-3.80 (0.4)	-2.90 (0.6)	0.25
Motor Subscore			
Primary analysis – Adjusted mean decline (SD)	-5.89 (1.09)	-4.64 (1.57)	0.526
Post hoc analysis – Adjusted mean decline (SD)	-5.50 (1.0)	-5.40 (1.5)	0.98
Respiratory Subscore			
Primary analysis – Adjusted mean decline (SD)	-1.70 (0.66)	-2.65 (0.93)	0.41
Post hoc analysis – Adjusted mean decline (SD)	-1.50 (0.6)	-3.00 (0.9)	0.21

Table 5: Estimated mean difference on the change of the ALSFRS-R subscore from V0 to 6 months – Post hoc analysis

- Decline in SVC was lower in the IFB-088 arm although the difference was not statistically significant (-22.8 vs -28.1 points, adjusted mean difference: 5.31 (95%CI: -9.72; 20.34), p=0.481
- The differences in rates of non-progressors according to King's College and ALS MITOS scores were not statistically significant.
- ALSAQ-40 scores increased in a similar manner in both groups, showing worsening over time (+ 25.4 ± 23 points in IFB-088 arm, n=23 vs 21.2 ± 19.3 points in placebo arm, n=16)

Safety

- Mean study duration was 196.0 (SD: 51.1) and 226.2 (SD: 7.1) days, mean total treatment duration was 161.7 (SD: 40.9) and 184.1 (5.4) days in the IFB-088 and in the placebo groups, respectively.
- Mean treatment compliance was 99.7 % (SD: 3.6) and 98.8 % (SD: 2.7) in the IFB-088 and in the placebo groups, respectively.
- In total, 7 deaths occurred during the study, including 5 and 2 in the IFB-088 and placebo arms respectively. Two sudden deaths, occurring in the IFB-088 arm were deemed possibly related to study drug since the exact cause of death could not be identified in the absence of autopsy. Fourteen SAEs were reported by 12 patients. The rate of SAEs was similar in both arms (23.5 %). In general, most AEs were mild or moderate in intensity. All grade gastrointestinal AEs were more frequent in the IFB-088 arm than in the placebo arm (35.3 vs 11.8 %). No AE led to study withdrawal.

	IFB-088, n=34		Placebo, n=17	
Patients with at least one	**Event**	**N (%)**	**Event**	**N (%)**
TEAE	71	25 (73.5)	28	10 (58.8)
SAE	9	8 (23.5)	5	4 (23.5)
Grade 1	41	19 (55.9)	16	7 (41.2)
Grade 2	18	11 (32.4)	8	5 (29.4)
Grade ≥3	12	10 (29.4)	4	3 (17.6)
SAE grade ≥3	8	8 (23.5)	2	2 (11.8)
Deaths, n (%)	5	5 (14.7)	2	2 (11.8)
Related to disease progression	3	3 (8.8)	2	2 (11.8)
Other (sudden deaths)	2	2 (5.9)	0	0 (0)
AEs reported by at least 15 % of patients in either arm				
Gastrointestinal disorders	14	12 (35.3)	3	2 (11.8)
Infections and infestations	15	8 (23.5)	9	5 (29.4)
Covid-19	3	3 (8.8)	2	2 (11.8)
Respiratory, thoracic and mediastinal disorders	7	5 (14.7)	4	4 (23.5)
Injury and procedural complications	15	8 (23.5)	0	0 (0)
Surgical and medical procedures	2	2 (5.9)	3	3 (17.6)
Serious adverse events				
Total	9	8 (23.5)	5	4 (23.5)
Infections and infestations	2	2 (5.9)	3	3 (17.6)
Covid-19	0	0 (0)	1	1 (2.0)
Respiratory, thoracic and mediastinal disorders	4	4 (11.8)	1	1 (5.9)
Cardiac disorders	2	2 (5.9)	0	0 (0)
General disorders and administration site conditions	0	0 (0)	1	1 (5.9)
Surgical and medical procedures (hospitalization)	1	1 (2.9)	0	0 (0)

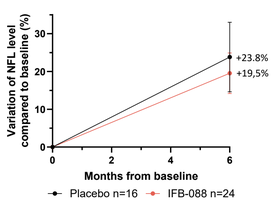
Table 2: Summary of adverse events, FAS population, n=51

Biomarkers

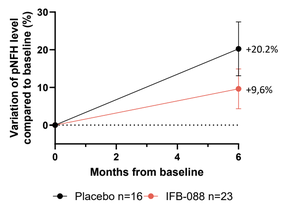
The 6-month treatment with IFB-088 significantly reduced:
- the increase of p75ECD level in urine (neurodegeneration biomarker);
- the increase of Neopterin level in urine (inflammation biomarker);
- the level of TGF-β1 in plasma (inflammation biomarker);
- the level of TDP-43 in plasma exosomes, reflecting the decrease of TDP-43 cytoplasmic mislocalization in ALS patients.

Neurodegeneration biomarkers

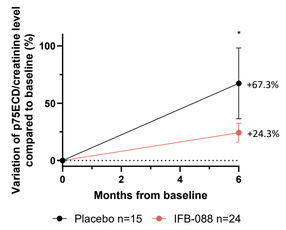
Plasmatic NfL level



Plasmatic p-NfH level

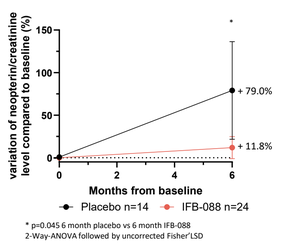


Urinary p75ECD/creatinine level

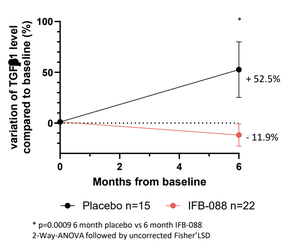


Inflammation biomarkers

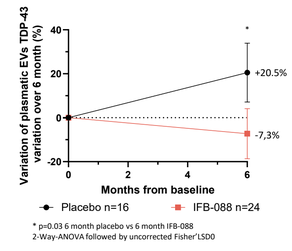
Urinary neopterin/creatinine level



Plasmatic TGFβ1 level



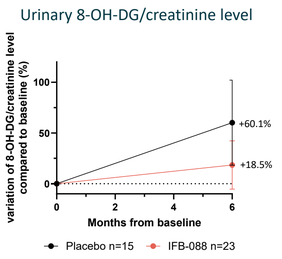
TDP-43 level in plasmatic extracellular vesicles (Evs)



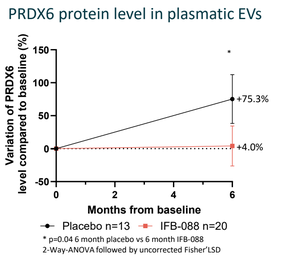
It allowed slowing:
- The decrease of 8-OHdG level in urine (oxidative stress biomarker).
- The decrease of UPR/ISR molecular markers, such as chaperones Bip and DnaJC7

Oxidative stress biomarkers

Urinary 8-OH-DG/creatinine level

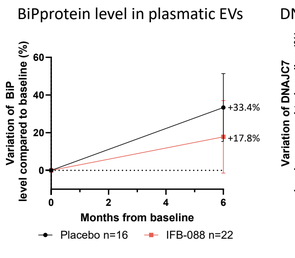


PRDX6 protein level in plasmatic EVs

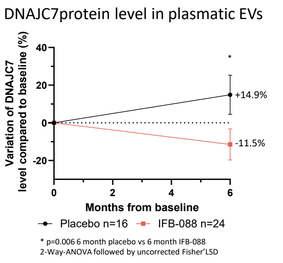


ISR biomarkers

BiPprotein level in plasmatic EVs



DNAJC7protein level in plasmatic EVs



Conclusion

- IFB-088 confirmed a favorable safety profile. Although the study was not powered to demonstrate efficacy, signals of positive effects were observed with a lower ALSFRS-R decline in the IFB-088 arm in the FAS and PP populations in the post hoc analysis conducted to compensate for an inclusion bias disadvantaging IFB-088: the slowing of ALSFRS-R decline over the 6-month TRIAL study in the PP population reached the pre-specified 2-sided level of significance of 0.20 (p=0.11) and is clinically meaningful. Benefits seem to be driven by a lower decline in respiratory function.
- Biomarker analysis confirms first-in-class mechanism of actions of IFB-088 on Integrated Stress Response and Oxidative Stress. IFB-088 is a multifunctional molecule able to target major cellular disease mechanisms implicated in ALS : TDP-43 mis-localization, oxidative stress, neurodegeneration and inflammation.