A Phase II randomized, multi-center study to evaluate the efficacy and safety of the oral single strain Live Biotherapeutic Product (LBP) Blautix in subjects with IBS-C and IBS-D

Alex Stevenson[1], Axel Glasmacher[1,2], Louise Markinson[1], Charlie Badham[1], Eamonn MM Quigley[3]

[1]4D pharma plc, Leeds, UK; [2]University of Bonn, Germany; [3]Co-ordinating Investigator, Houston Methodist Hospital and Weill Cornell Medical College, Houston, Tx, USA

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BACKGROUND AND RATIONALE

- Current IBS treatments target subtype-specific symptoms of either IBS with constipation (IBS-C) or diarrhea (IBS-D).
- Safety and tolerability is a common concern for both patients and clinicians regarding current treatment option, often as a consequence of symptom-targeted mechanisms of action.
- Blautix (*Blautia hydrogenotrophica*) is an oral single strain Live Biotherapeutic Product (LBP) and potential disease-modifying therapy for multiple IBS subtypes.
- LBPs are a novel class of drug, defined as a biological product that contains live organisms such as bacteria for the prevention, treatment, or cure of disease, and that is not a vaccine.
- We conducted a Phase II randomized, double blind, placebo-controlled, parallel group, multi-center, study in adult patients with IBS-C or IBS-D, to evaluate the safety and clinical efficacy of Blautix on key features of IBS and to define key parameters for a pivotal program.

STUDY DESIGN

- Parallel cohorts of 164 IBS-C patients and 201 IBS-D patients in US, UK and Ireland were randomized 1:1 to receive twice-daily Blautix (>1 × 10^{10} most probable number (MPN)) or placebo for 8 weeks.
- The primary efficacy analysis was the overall responder rate (ORR) in all randomized patients with eligible baseline data in each cohort (N=353).
- To be an 'overall responder' required:

IBS-C	IBS-D
Weekly improvement in **abdominal pain**: decrease of ≥30% vs baseline; and	
Weekly improvement in **stool frequency**: an increase of ≥1 complete spontaneous bowel movement per week vs baseline	Weekly improvement in **stool consistency**: a decrease of ≥50% in proportion of days with ≥1 stool of Type 6-7 by Bristol Stool Scale vs baseline
Concurrently in the same week ('weekly responder')	
For **≥4 out of 8** treatment weeks ('**overall responder**')	

Table 1: Description of overall responder composite primary endpoint.

- Statistical testing of ORR, abdominal pain intensity and bowel habit (stool frequency or consistency) was 1-sided and performed at the 0.10 significance level, Pearson's test with Yates's correction.
- The primary endpoint was also assessed in all patients evaluable for efficacy at 8 weeks (N=316).
- Post-hoc analyses were conducted to identify sub-groups displaying enhanced response.
- Statistical testing of other efficacy endpoints was 2-sided and performed at the 0.05 significance level. Adjustments were not made for multiple testing.

The study was sponsored by **4D pharma plc**. For more information, contact clinicaltrials@4dpharmaplc.com. www.ClinicalTrials.gov: NCT03721107

PATIENT CHARACTERISTICS

The study recruited adult male and female subjects aged 18-70 with BMI of 18-39 kg/m^2; diagnosis of IBS-C or IBS-D as defined by Rome IV; moderate or severe IBS symptom severity score (IBS-SSS) ≥175 at screening. No significant differences between Blautix and placebo arms at baseline in either cohort.

	IBS-C		IBS-D	
	Blautix	Placebo	Blautix	Placebo
Male (N) [1]	13	15	37	31
Female (N) [1]	67	69	60	73
Mean Age (± SD) [1]	44.6 (13.04)	45.3 (13.41)	43.1 (13.65)	44.9 (14.40)
Mean BMI (± SD) [1]	28.28 (5.30)	28.13 (5.00)	28.25 (5.24)	28.26 (4.97)
USA (N) [2]	57	65	50	55
UK & IRE (N) [2]	19	17	44	46
Weekly average abdominal pain intensity (± SD) [1]	6.17 (1.56)	6.05 (1.48)	5.93 (1.61)	5.45 (1.45)
Weekly average stool frequency [1]	1.71 (0.53)	1.68 (0.60)	10.72 (2.99)	11.15 (3.35)
% of days with stool of interest (± SD) [1, 3]	22.43 (8.00)	21.57 (8.56)	83.14 (17.01)	84.26 (16.64)
Mean baseline IBS-SSS (± SD) [2]	381.58 (67.89)	390.92 (59.59)	361.81 (71.85)	347.17 (79.06)

Table 2: Patient characteristics. *[1] All patients that received ≥1 dose Blautix or placebo. [2] Randomized patients with eligible baseline data. [3] IBS-C: ≥1 stool of consistency 1 or 2 on Bristol Stool Scale (BSS); IBS-D: ≥1 stool of consistency 6 or 7 on BSS.*

RESULTS - SAFETY

Blautix demonstrated a safety profile comparable to placebo.

- Frequency of AEs comparable to placebo.
- No treatment-related severe or serious AEs reported.
- Most frequent possibly treatment-related AEs occurring in >1 patient and at greater frequency in Blautix than placebo arms (IBS-C and IBS-D combined): diarrhea (2.8%), dyspepsia (1.7%), abdominal pain (1.7%), headache (1.7%) IBS (1.1%), vomiting (1.1%).

	Blautix	Placebo
All adverse events (AEs)	58 (32.8%)	62 (33.0%)
All treatment-related AEs (TREAs)	21 (11.9%)	18 (9.6%)
Severe adverse events	1 (0.6%)	2 (1.1%)
Treatment-related severe adverse events	0	0
Serious adverse events (SAEs)	1 (0.6%)	1 (0.5%)
Treatment-related SAEs	0	0
AEs leading to treatment discontinuation	7 (4%)	6 (3.2%)

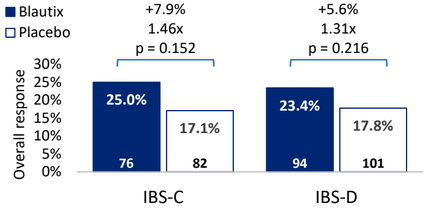
Table 3: Summary of AEs. *All patients that received ≥1 dose Blautix or placebo, IBS-C and IBS-D cohorts combined.*

RESULTS - EFFICACY

Figures above brackets on bar charts represent, in vertical order, delta Blautix vs placebo, relative response Blautix vs placebo, p value; N at base of bar

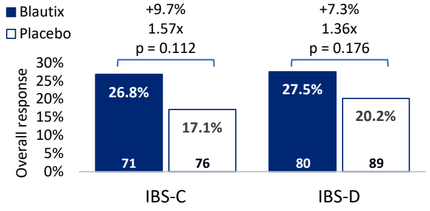
A) Overall responder rate, all randomized patients (N=353)

- IBS-C: 46% relative increase in ORR vs placebo
- IBS-D: 31% relative increase



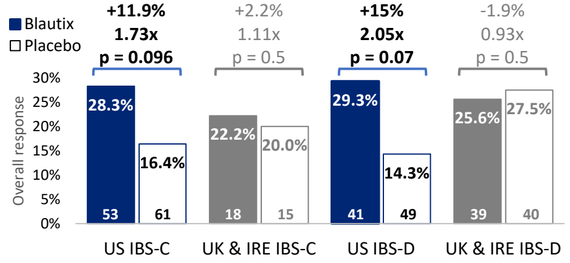
B) Overall responder rate, patients evaluable for efficacy (N=316)

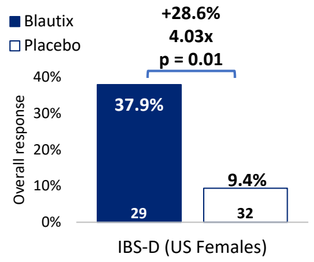
- IBS-C: 57% relative increase in ORR vs placebo
- IBS-D: 36% relative increase



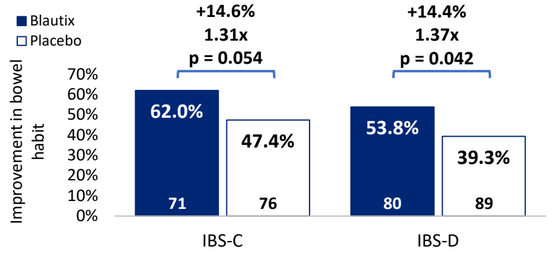
C) Pre-planned analysis of overall responder rate by region identified markedly greater placebo response rates in UK & Ireland vs US (patients evaluable for efficacy).

- In US patients, Blautix showed clinically meaningful positive trends in IBS-C and IBS-D.
- In the major subpopulation of female IBS-D patients there was an enhanced, statistically significant ORR

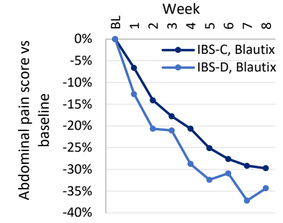




D) Bowel habit. Clinically meaningful and statistically significant improvement in bowel habit in IBS-D, nearing significance in IBS-C, in patients evaluable for efficacy.



E) Abdominal pain reduced from baseline (BL) in IBS-C and IBS-D patients receiving Blautix.



CONCLUSIONS

- **Blautix demonstrated a safety profile comparable to placebo.**
- **Patients recruited in UK & Ireland exhibited markedly higher placebo response rates than in US, negatively impacting the primary endpoint.**
- **In US, a strong positive trend in overall response was observed for *both* IBS-C and IBS-D.**
- **Enhanced, statistically significant ORR observed in female US IBS-D patients, the larger gender sub-population.**
- **Clinically meaningful and statistically significant improvements in bowel habit in IBS-D, nearing significance in IBS-C; a potential primary endpoint to support regulatory approval.**
- **Relative response rates vs placebo observed in this small signal finding Phase II are highly encouraging for subsequent larger studies with increased statistical power.**
- **Overall responder rates and bowel habit improvement in both IBS-C and IBS-D cohorts indicate Blautix as a potential treatment option for all IBS subtypes, including IBS-M (mixed).**