4D pharma plc

developing science
delivering therapies

BHT-II-002: Phase II trial of Live Biotherapeutic Blautix for IBS

7 October 2020

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KEY TAKEAWAYS

What we set out to achieve

- BHT-II-002 was a Phase II study designed to generate a meaningful signal of clinical activity in IBS-C and IBS-D and combined populations and to provide the necessary data for a pivotal development program

What we saw

- Blautix demonstrated an effect size relative to placebo comparable to pivotal studies of approved products in **both** IBS-C and IBS-D
- Blautix demonstrated activity in a combined cohort of IBS-C and IBS-D patients
- Blautix showed a safety profile comparable to placebo
- Preliminary evidence of enhanced activity in specific sub-groups
- Significant signal in overall improvement of bowel habit across both sub-types

Where we go next

- Data highly encouraging and supportive of progressing the candidate towards pivotal Phase III trials
- Unique potential to address all sub-types of the disease, including IBS-M

"The prospect of a treatment that equally benefits both IBS-C and IBS-D with a strong safety profile is very compelling."

Prof. Eamonn Quigley, Head of Gastroenterology and Hepatology, Houston Methodist Hospital, BHT-II-002 Chief Investigator

Blautix®

Single strain Live Biotherapeutic product (LBP)

Blautia hydrogenotrophica

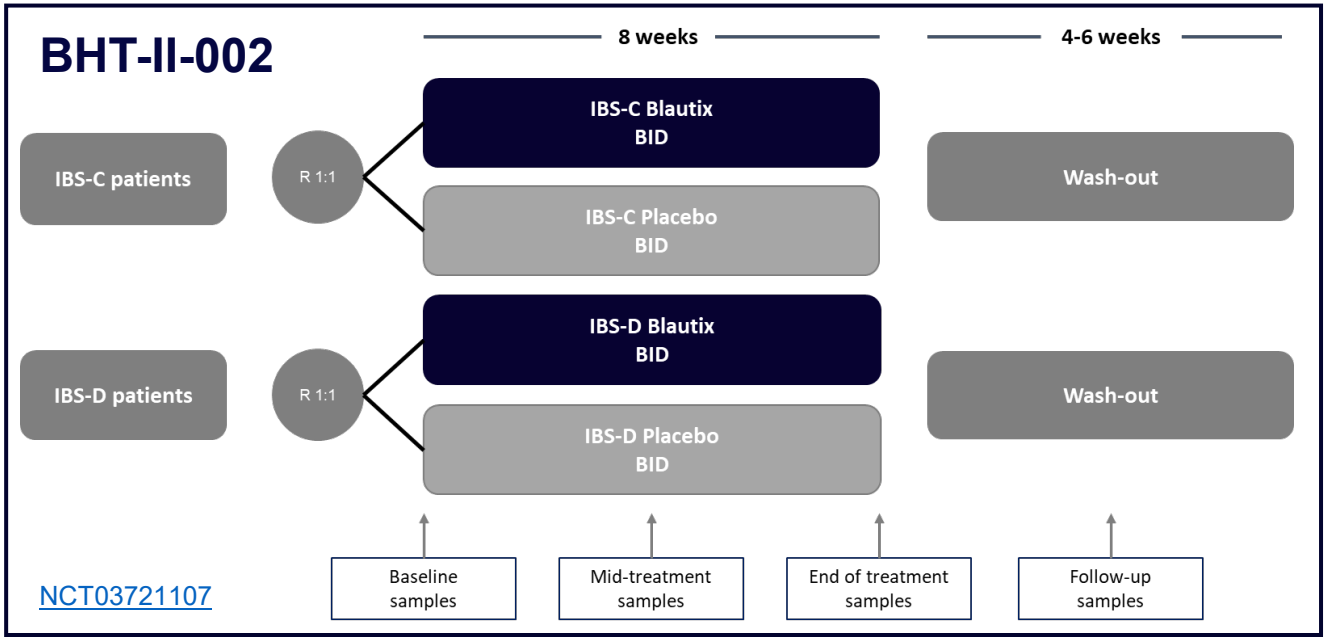
~10^{10} CFU per capsule

Manufactured in-house (see: here for details of manufacturing process and capabilities.)

Patent coverage out to 2036

Four patent families, including granted patents in the US, Europe and Japan

BHT-II-002: INVESTIGATION OF SIGNALS IN IBS WITH BLAUTIX®



- Phase II randomised placebo-controlled study, designed with FDA feedback
- Objective to generate data to guide subsequent pivotal development phase
- IBS-C or IBS-D as defined by Rome IV criteria
- Each cohort randomised 1:1 to receive either Blautix® or placebo
- Orally administered, 2 capsules twice daily for 8 weeks

TRIAL OVERVIEW: EVALUATING THE EFFICACY OF BLAUTIX®

Study endpoints

Primary: **Overall response rate**

To be an 'overall responder' patients must have:

improvement in their weekly, abdominal pain intensity *and* stool frequency (IBS-D) *or* consistency (IBS-C);

for ≥50% of the treatment period

Additional analyses of the primary endpoint include:

Response rate in combined IBS-C/D group

Analysis of bowel habit and pain independently

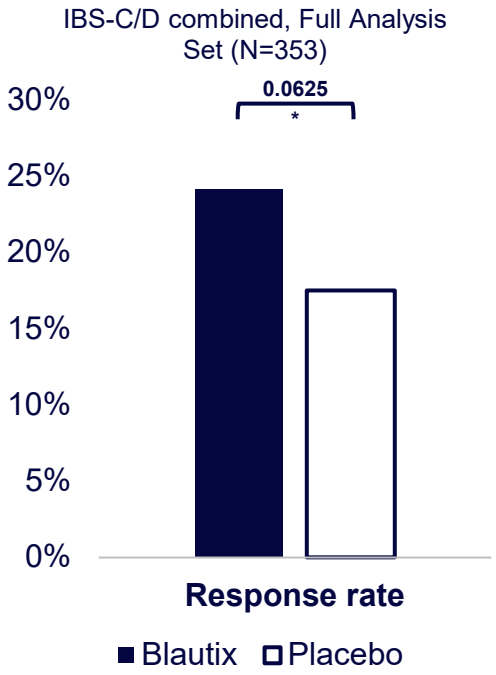
Patient overview

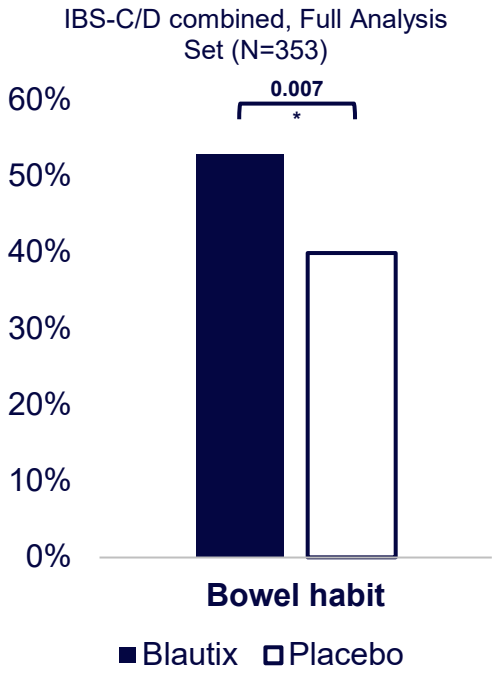
- 353 patients randomized and with eligible baseline criteria
  - 158 IBS-C
  - 195 IBS-D
  - 64% of patients US
  - 75% of patients female
- Primary endpoint calculations based on Full Analysis Set (FAS) [1]
- All endpoints also assessed in Efficacy Evaluable Analysis Set (EEAS) [2]

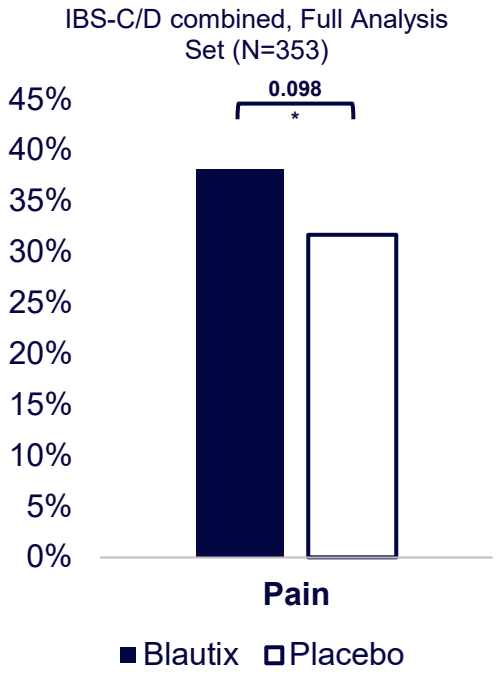
[1] Full Analysis Set (FAS) includes all subjects randomized into the study

[2] Efficacy Evaluable Set (EES) includes all members of the FAS who completed the 8-week treatment and assessment period without major protocol violations deemed to impact the assessment of efficacy

BLAUTIX® vs PLACEBO: COMBINED GROUP







Differential to placebo:

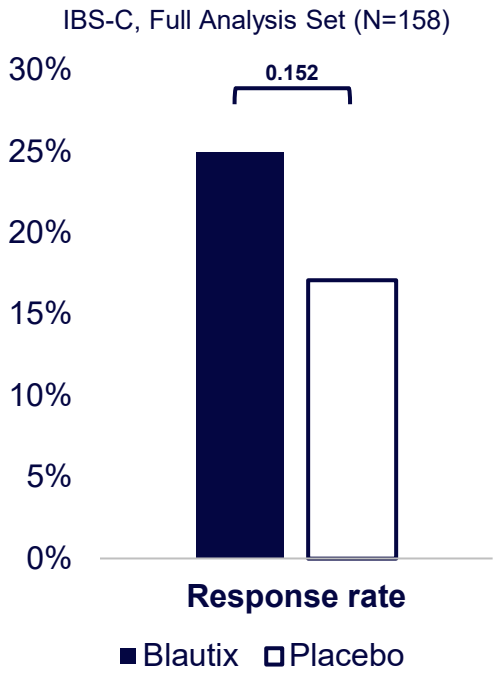
- Overall response rate of 6.6%
- Improvement in bowel habit of 13.1%
- Improvement in abdominal pain of 6.5%

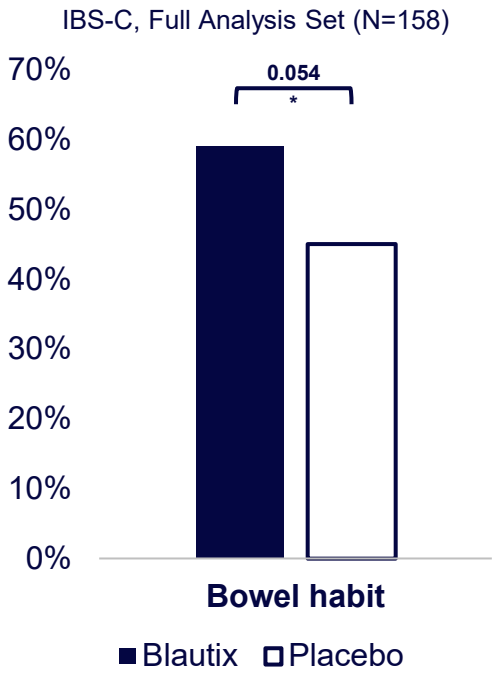
Points of interest:

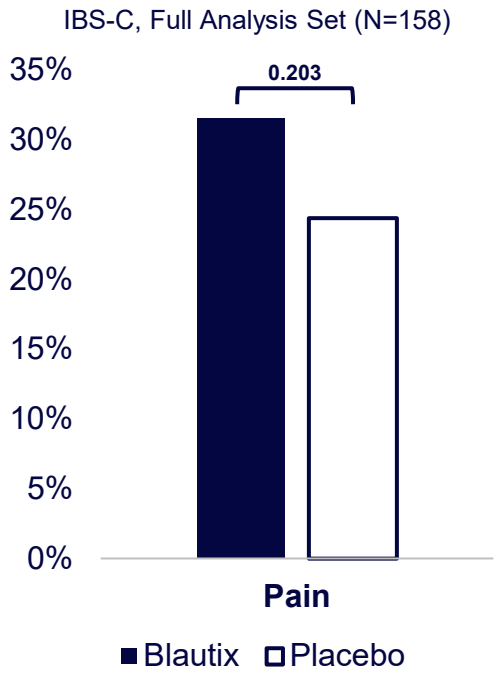
- No existing single agent that addresses both IBS-C, IBS-D or IBS-M
- EEAS response rate shows 8.4% differential to placebo, p=0.037

* Significance level 0.1, 1-sided Pearson chi-squared test with Yates' correction; no correction for multiple analyses is applied

BLAUTIX® vs PLACEBO: IBS-C







Differential to placebo:

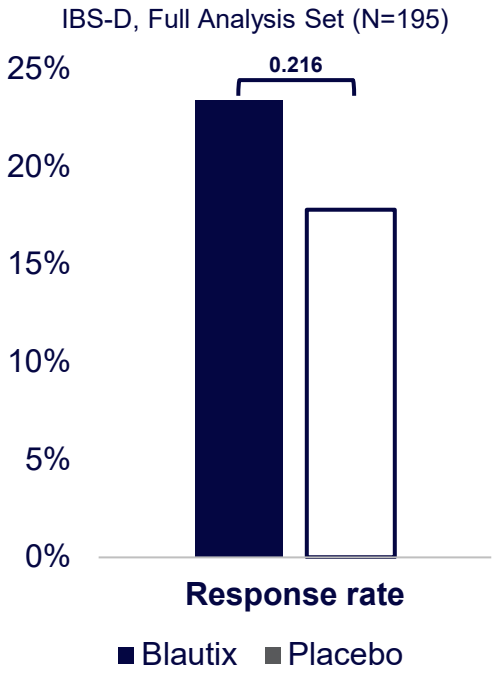
- Overall response rate of 7.9%
- Improvement in bowel habit of 14.1%
- Improvement in abdominal pain of 7.2%

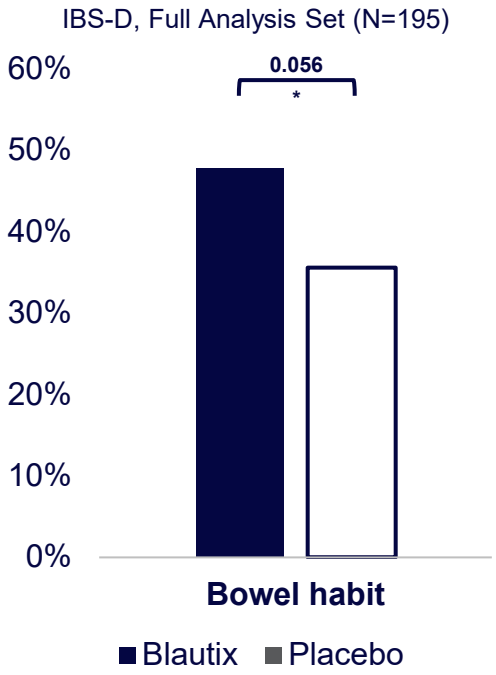
Points of interest:

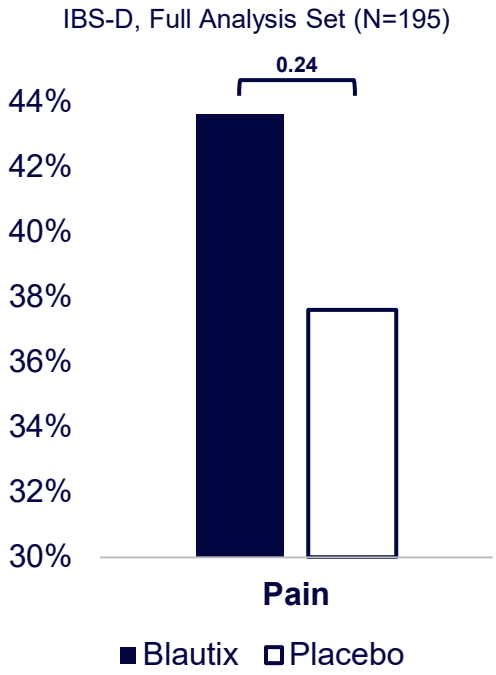
- Total of 76 patients received Blautix®
- EEAS response rate shows 10.1% differential to placebo, p=0.097

* Significance level 0.1, 1-sided Pearson chi-squared test with Yates' correction; no correction for multiple analyses is applied

BLAUTIX® vs PLACEBO: IBS-D







Differential to placebo:

- Overall response rate of 5.6%
- Improvement in bowel habit of 12.2%
- Improvement in abdominal pain of 6.0%

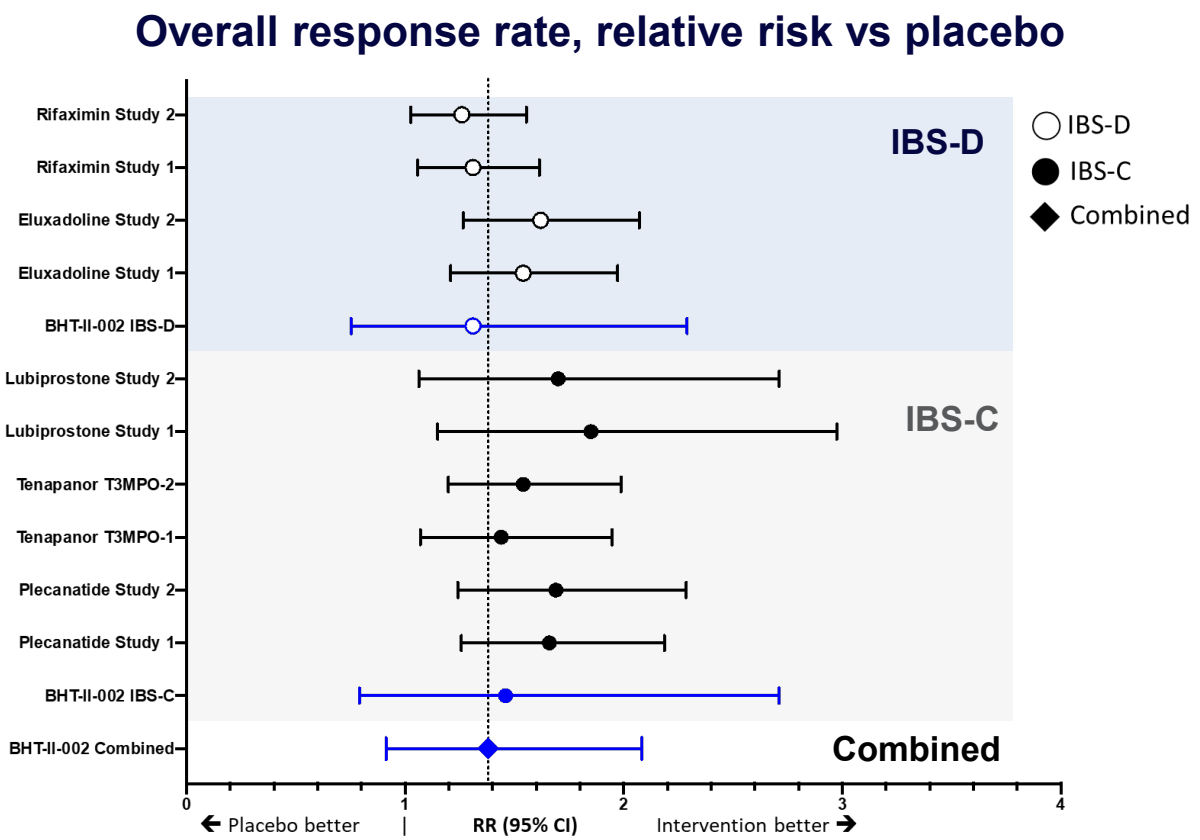
Point of interest:

- 94 IBS-D patients received Blautix®
- EEAS response rate shows 6.9% differential to placebo, p=0.188

* Significance level 0.1, 1-sided Pearson chi-squared test with Yates' correction; no correction for multiple analyses is applied

COMPARABLE EFFICACY TO APPROVED IBS PRODUCTS

- Blautix relative risk vs placebo in Phase II is within confidence limits of pivotal trials of IBS products
- In both IBS-C and IBS-D
- Comparator studies typically 3-5x size of Phase II BHT-II-002

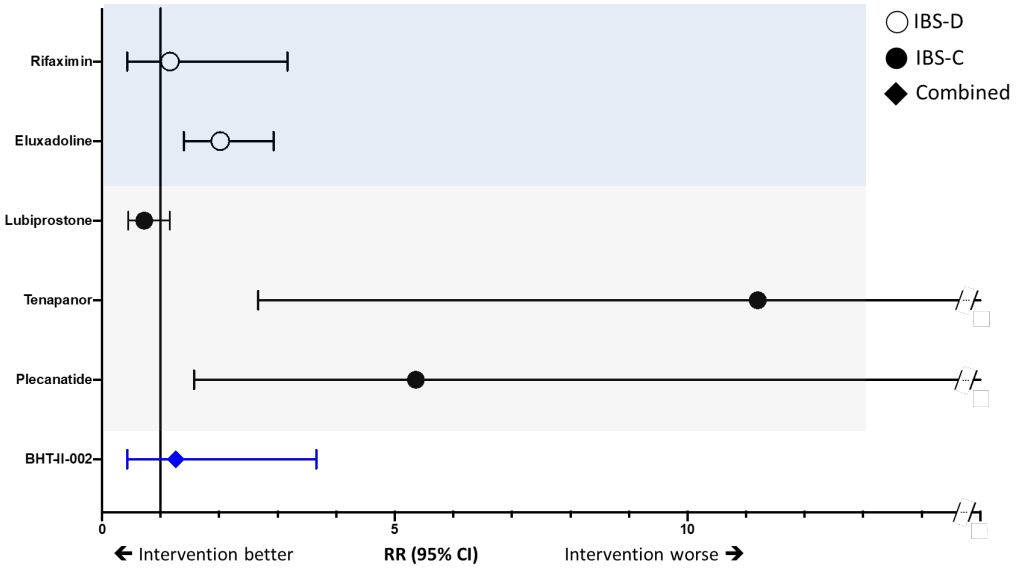


- **Strong result from signal finding Phase II to support Phase III development**

BLAUTIX® vs PLACEBO: NO DISCERNIBLE DIFFERENCE IN SAFETY

- All adverse events (AEs) [1]
  - Blautix 32.8% vs placebo 33.0%
- All severe adverse events
  - Blautix N=1, 0.6% vs placebo N=2, 1.1%
  - No treatment-related severe adverse events
- All serious adverse events (SAEs) [2]
  - Blautix N=1 0.6% vs placebo N=1 0.5%
  - No treatment-related SAEs recorded

Treatment discontinuation due to AEs (Relative risk vs placebo)



[1] AE defined as an adverse event that started or worsened in severity on or after the start date of the study drug and includes all adverse events recorded through the follow-up visit

[2] A serious AE is any AE that is life-threatening, results in death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. *US FDA Title 21, Chapter I, Subchapter D, Part 312. Subpart B, 312.32 IND safety reporting.* Severity is a grading of any AE (mild, moderate or severe). A serious AE can be mild, and a non-serious AE can be severe

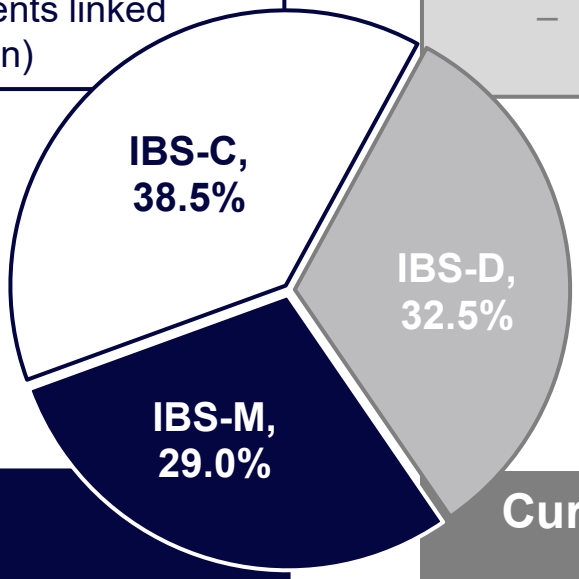
MARKET STATISTICS AND US PATIENT POP BY SUBTYPE

IBS-C

- Estimated ~1.7m US cases treated 2019
- Leading blockbuster IBS-C therapeutic – linaclotide
  - High % of adverse events linked to MoA (diarrhoea, pain)

IBS-D

- Estimated ~1.4m US cases treated 2019
- Leading IBS-D therapeutic - rifaximin
  - Antibiotic - possible for patients to develop resistance



IBS-M

- **Significant commercial opportunity**
- No approved therapeutic regime
- Clinicians dilemma

Current Market IBS-C and IBS-D

- Incidence of IBS in US ≈ **10-15%**
- **60%** of all IBS patients are female
- Estimate US market 2024: **$2.4bn**

GLOBALDATA IBS MARKET ANALYSIS TO 2026: KOL COMMENTS

"In terms of IBS-M, we have really nothing much to offer them. That is a huge unmet need, and there is no medication approved by the FDA or the EMA for this condition."

"None of the IBS drugs available on the market work perfectly for all IBS patients. So, the unmet need is having better drugs."

"It can be challenging to treat IBS-M, because patients have different symptoms on different days. It is less clear how to treat IBS-M patients."

"Most patients get a single script [prescription], and then never touch the drug ever again, because they stop using it, and it is just sitting in their cabinet."

BLAUTIX : PLANNING TO BRING NEW SOLUTION TO IBS MARKET

Issue	Solution	Blautix®
30% of patients currently underserved as fall into neither IBS-C or IBS-D	Address Combined IBS-C and IBS-D subtypes	BHT-II-002 primary endpoint met in **IBS-C/D combined** group *and* strong trends in **individual subgroups**
Clinician concern over safety of current treatment options	Address concerns over side effect	Safety profile **comparable** to placebo
Poor patient compliance	Address key concerns over debilitating symptoms	**Placebo-like tolerability** *and* strong trends in **improvement of bowel habits**

- ***The first therapy to show signals of efficacy in both IBS-C and IBS-D***
- ***Blautix has the potential to be first ever therapy for IBS–M patients***
- ***Analysis of Phase II BHT-II-002 to inform larger Phase III pivotal trial***

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