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4D pharma Virtual R&D Event, 25 May 2021

Phase II trial of Live Biotherapeutic Blautix for IBS-C and IBS-D

Digestive Disease Week 2021

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4D pharma - OUR VISION

Leveraging the power of the microbiome to lead a revolution in drug development, discovering and developing safe, innovative Live Biotherapeutic Products (LBPs)

Developing science, delivering therapies

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BLAUTIX® – A NOVEL APPROACH TO IBS

Blautix® (MRx1234)

Single strain Live Biotherapeutic product (LBP)

Blautia hydrogenotrophica

Orally administered

Does not require antibiotic pre-treatment, bowel prep, or colonization for therapeutic activity

MoA: H_2 & H_2S consumption; acetate production

Manufactured at in-house cGMP facility

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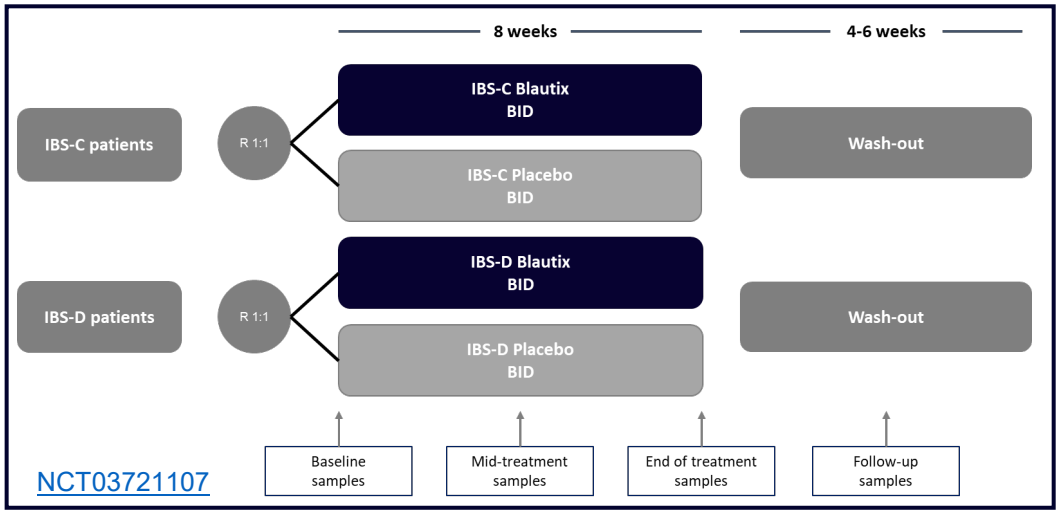
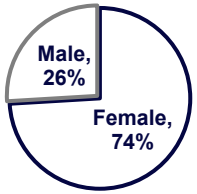
BHT-II-002: INVESTIGATION OF SIGNALS IN IBS WITH BLAUTIX®

Phase II randomised, placebo-controlled, multi-centre study



- Inclusion criteria: diagnosed with IBS-C or IBS-D as defined by Rome IV criteria; moderate or severe IBS symptom severity score (>175) as defined by IBS-SSS
- N=316 patients evaluable for efficacy having completed the full 8-week treatment and assessment period

	IBS-C	IBS-D
Blautix	71	80
Placebo	76	89



Efficacy Evaluable Analysis Set (EEAS), all randomized patients with eligible baseline data that completed the 8-week treatment and assessment period without major protocol violations deemed to impact the assessment of efficacy, identified in blinded data review

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PHASE II TRIAL OVERVIEW: COMPOSITE PRIMARY ENDPOINT

Complex primary endpoint: **overall response rate** in IBS-C and IBS-D cohorts

To be an 'overall responder' patients must have:

- Improvement in their weekly
  - Abdominal pain intensity (decrease of ≥30% vs baseline); *and*
  - Stool frequency (IBS-C) (increase of ≥1 CSBM per week vs baseline); *or*
  - Stool consistency (IBS-D) (decrease of ≥50% in the proportion of days with ≥1 stool of Type 6-7 by BSS vs baseline);
- Concurrently, for ≥50% of the treatment period

Illustrative examples of the complexities of the 'overall responder' composite endpoint:

Symptom	*Week 1*	*Week 2*	*Week 3*	*Week 4*	*Week 5*	*Week 6*	*Week 7*	*Week 8*	Weekly responder	Overall responder?
Bowel habit	Y	Y	Y	Y	Y	Y	N	N	6/8	3/8 (<50%) **No**
Abdominal pain	N	N	N	Y	Y	Y	Y	Y	5/8	

Endpoint	*Week 1*	*Week 2*	*Week 3*	*Week 4*	*Week 5*	*Week 6*	*Week 7*	*Week 8*	Weekly responder	Overall responder
Bowel habit	Y	Y	Y	Y	Y	Y	Y	Y	8/8	0/8 (<50%) **No**
Abdominal pain	N	N	N	N	N	N	N	N	0/8	

Endpoint	*Week 1*	*Week 2*	*Week 3*	*Week 4*	*Week 5*	*Week 6*	*Week 7*	*Week 8*	Weekly responder	Overall responder
Bowel habit	Y	N	Y	N	Y	N	Y	N	4/8	4/8 (≥50%) **Yes**
Abdominal pain	Y	N	Y	N	Y	N	Y	N	4/8	

Endpoint	*Week 1*	*Week 2*	*Week 3*	*Week 4*	*Week 5*	*Week 6*	*Week 7*	*Week 8*	Weekly responder	Overall responder
Bowel habit	N	N	Y	N	Y	N	Y	Y	3/8	3/8 (<50%) **No**
Abdominal pain	Y	Y	Y	Y	Y	Y	Y	Y	8/8	

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CSBM – complete spontaneous bowel movements; BSS - Bristol Stool Scale

PHASE II TRIAL OVERVIEW: ANALYSIS OF ENDPOINTS

- Primary endpoint: **overall responder rate** in IBS-C and IBS-D cohorts independently

  Overall response is a composite endpoint comprising concurrent improvements in both major symptoms: bowel habit and abdominal pain

- Additional analyses of the primary endpoint included:
  - Overall response rate in **combined IBS-C/D group**
  - Analysis of **bowel habit** (stool frequency/consistency) independently
  - Analysis of **abdominal pain** independently
  - Analysis of endpoints in **regional** and **gender** sub-sets

- Previously announced topline results were assessed in all randomized patients (N=353)

- Endpoints also assessed in all patients evaluable for efficacy after 8 weeks of treatment – 'Efficacy Evaluable Analysis Set' (N=316)

  IBS-C, N=147

  IBS-D, N=169

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BLAUTIX PHASE II TRIAL IN IBS-C AND IBS-D: AIMS & OUTCOMES

Aims

- A signal finding Phase II to investigate activity of Blautix in the treatment of IBS-C and IBS-D
- Using FDA-recommended primary endpoint for registration of an IBS therapy
- To evaluate the safety of Blautix in IBS patients
- The study is the largest clinical trial of a Live Biotherapeutic product (LBP) conducted to date

Outcomes

- Excellent safety profile, indistinguishable from placebo
- First therapeutic to demonstrate activity in both IBS-C and IBS-D
- Notable differences in placebo response rate between study regions warrant further investigation
- Particularly strong effect in improving bowel habit observed, which could support approval as a primary endpoint according to FDA guidance
- Particularly strong effects in key sub-populations, e.g. female IBS-D patients

Results support continued development, with multiple routes to commercialization available and a potentially highly attractive and competitive product profile

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SAFETY - NO DIFFERENCE FROM PLACEBO

In the Phase II trial Blautix showed good safety and tolerability

- Comparable adverse event profile to placebo
- No treatment-related severe or serious adverse events

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

IBSC/D cohorts combined

[1] Ankle fracture, not treatment related. [2] Atrial fibrillation, not treatment related

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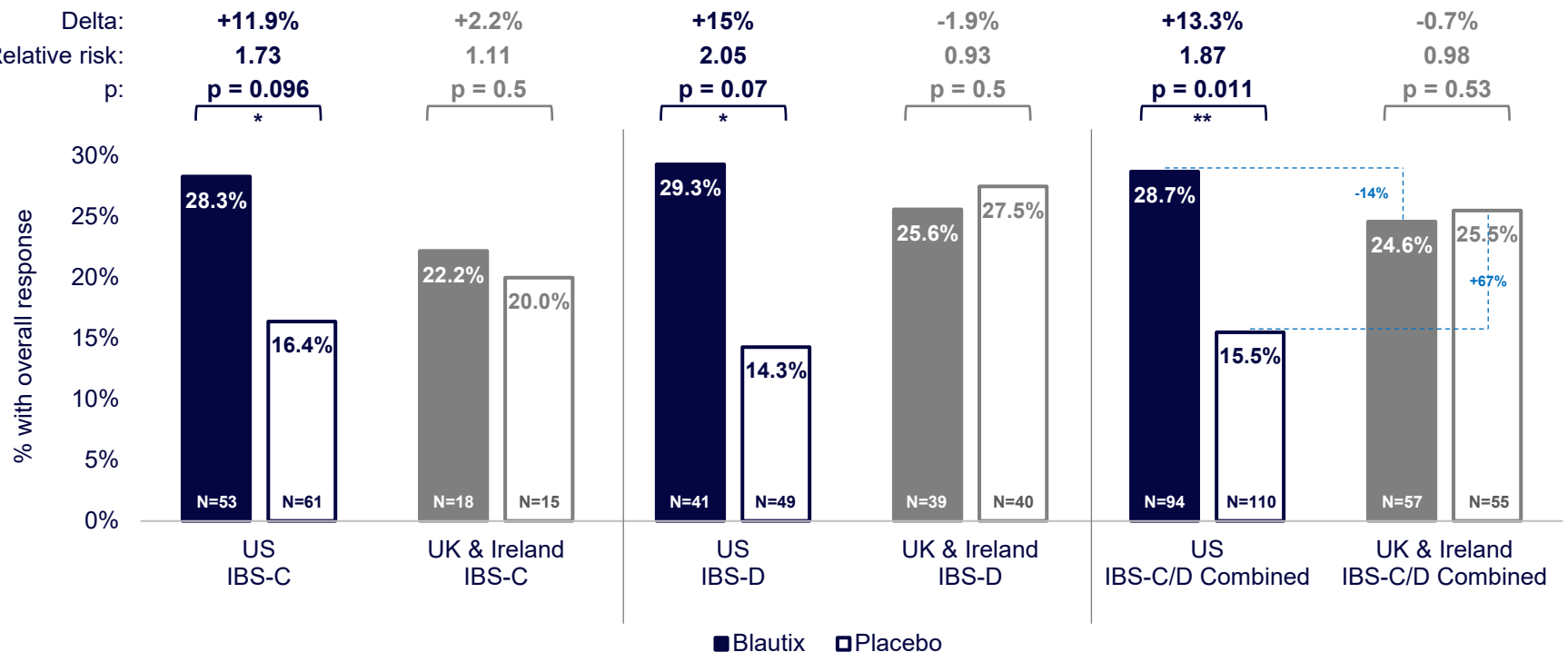
HIGH PLACEBO RESPONSE OBSERVED IN UK & IRELAND

- Considerably higher placebo response rate observed in UK & Ireland patients
- Blautix activity comparable across regions
- In US patients, statistically significant ORR in IBS-C/D combined analysis; strong, clinically meaningful trends in IBS-C and IBS-D cohorts
- All patients met same enrolment criteria; no significant differences in baseline characteristics
- 64% of Blautix Phase II patients recruited in US



EEAS. * Significance level P < 0.1, ** P < 0.05, *** P < 0.01. 1-sided Pearson chi-squared test with Yates' correction; no correction for multiple analyses is applied.
Relative risk vs placebo represents the relative increase of efficacy of the drug vs placebo, e.g. 1.45 represents a relative increase in efficacy of 45% vs placebo

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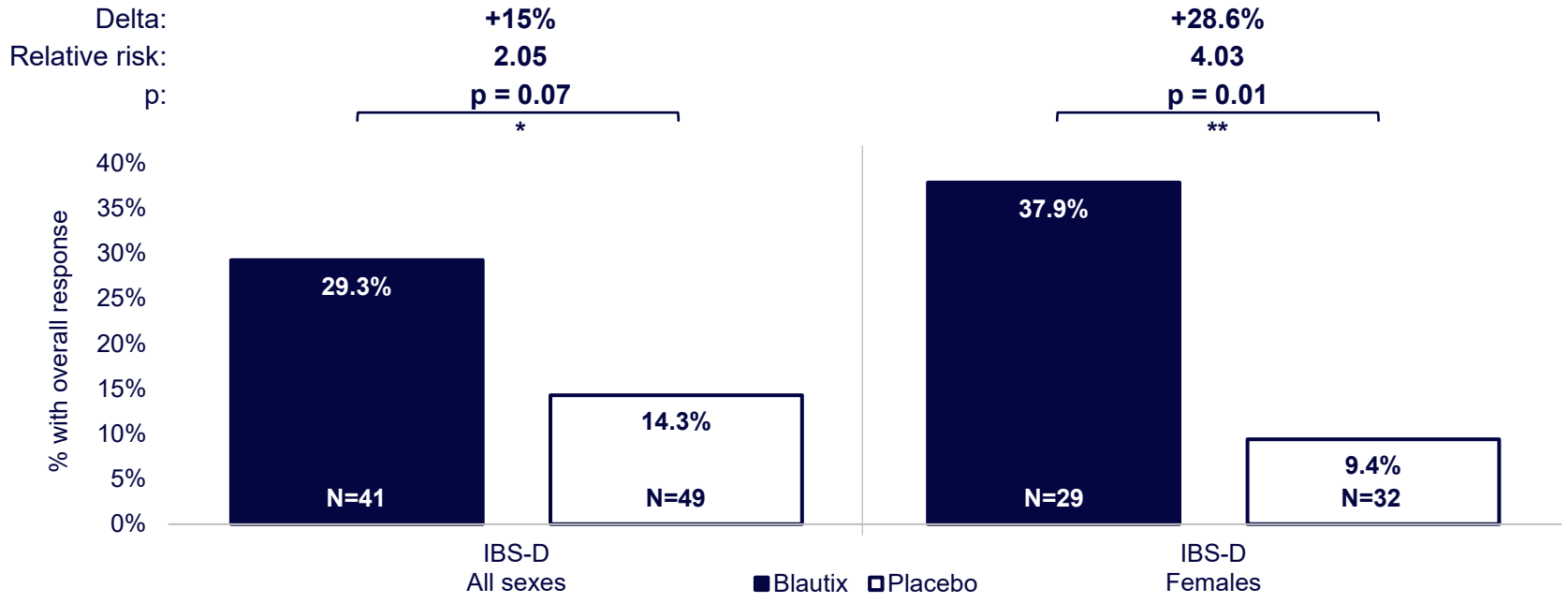
STRONG SIGNAL IN IBS-D, ENHANCED IN FEMALES

- Strong positive trend on primary endpoint of overall response rate (abdominal pain + bowel habit) in IBS-D
  - Over 2x improvement vs placebo, p=0.07
- Particularly strong, statistically significant overall response rate in female IBS-D subjects
  - Over 4x improvement vs placebo, p=0.01



EEAS, US patients. * Significance level P < 0.1, ** P < 0.05, *** P < 0.01.

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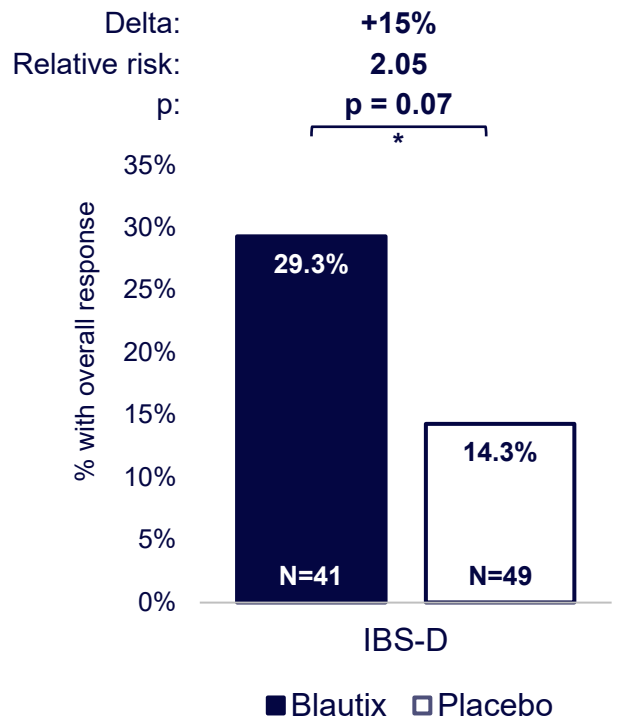
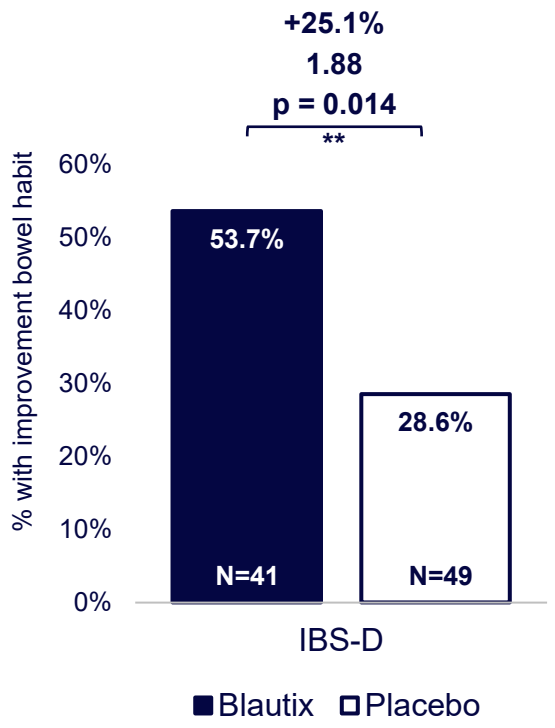
IBS-D: STRONG ORR SIGNAL, POTENTIAL FOR APPROVAL BASED ON BOWEL HABIT

FDA, Irritable Bowel Syndrome - Clinical Evaluation of Products for Treatment (2012). A drug can be specifically developed to treat only one of the major signs or symptoms of IBS [abdominal pain or bowel habit], which should be identified as the primary endpoint in the clinical trial. The other key efficacy endpoints should be assessed in the clinical trial as secondary endpoints. **Demonstration of significant and clinically meaningful changes in the targeted single endpoint could serve as a basis for approval, as long as the other important symptoms or signs have not worsened on treatment.**

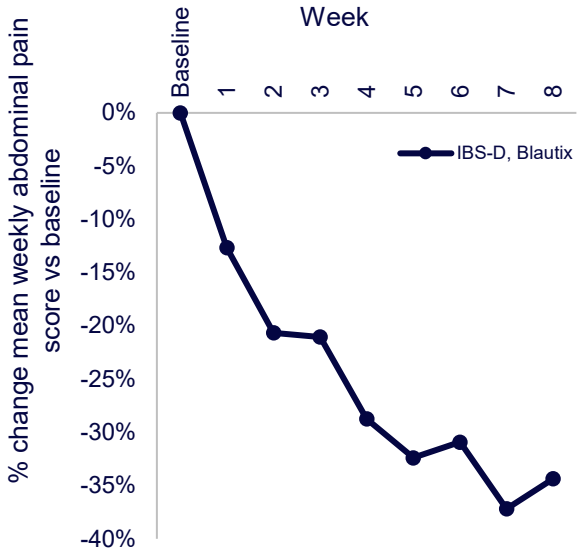
Strong positive trend in ORR (bowel habit + abdominal pain)



Statistically significant improvement in stool consistency



Positive effect in reducing abdominal pain



EEAS, US patients. * Significance level P < 0.1, ** P < 0.05, *** P < 0.01.

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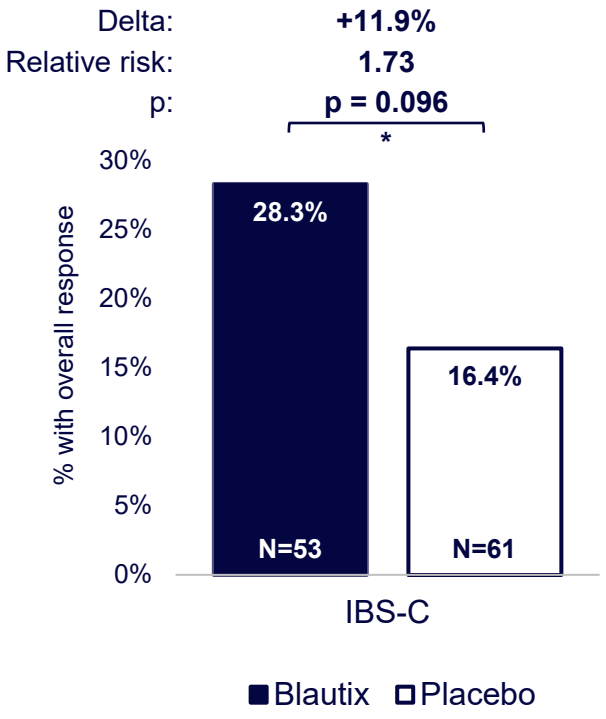
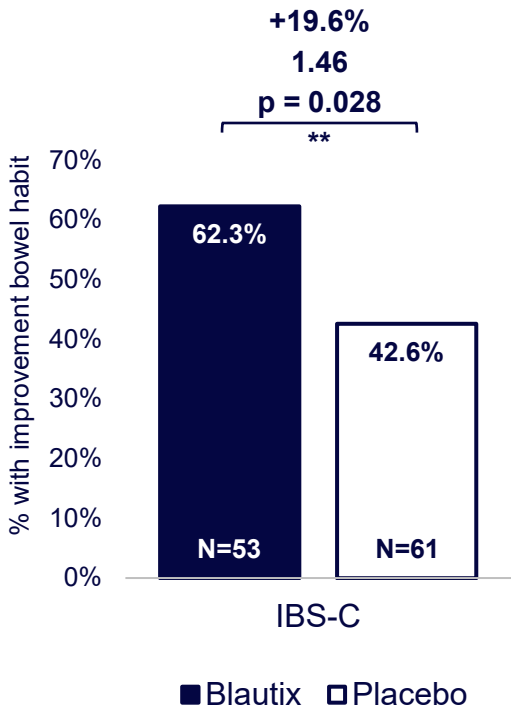
IBS-C: STRONG ORR SIGNAL, POTENTIAL FOR APPROVAL BASED ON BOWEL HABIT

FDA, Irritable Bowel Syndrome - Clinical Evaluation of Products for Treatment (2012). A drug can be specifically developed to treat only one of the major signs or symptoms of IBS [abdominal pain or bowel habit], which should be identified as the primary endpoint in the clinical trial. The other key efficacy endpoints should be assessed in the clinical trial as secondary endpoints. **Demonstration of significant and clinically meaningful changes in the targeted single endpoint could serve as a basis for approval, as long as the other important symptoms or signs have not worsened on treatment.**

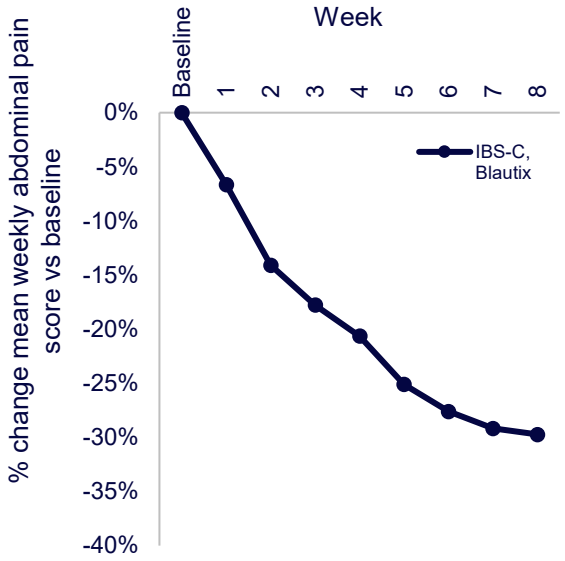
Strong positive trend in ORR (bowel habit + abdominal pain)



Statistically significant improvement in stool frequency



Positive effect in reducing abdominal pain



EEAS, US patients. * Significance level P < 0.1, ** P < 0.05, *** P < 0.01.

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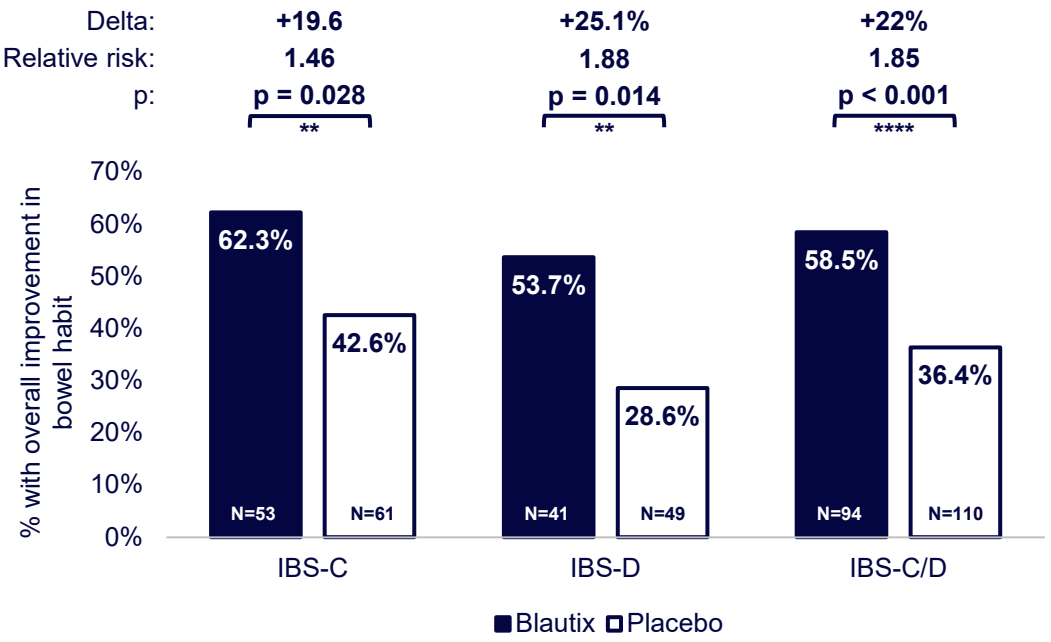
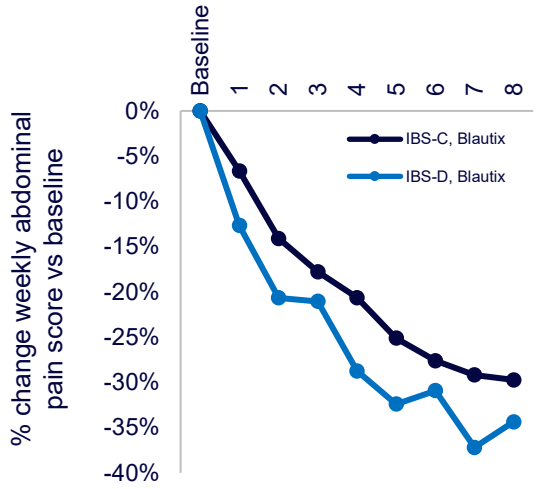
IBS-M: POTENTIAL FIRST-TO-MARKET OPPORTUNITY

- Investigation of bowel habit shows a particularly strong, statistically significant impact of Blautix across both subtypes
- And a positive trend in improvement in abdominal pain across all subtypes





- This unique activity indicates potential to treat **IBS-M (mixed)**, in which patients fluctuate between primary symptom of constipation or diarrhoea
- IBS-M is an area of significant unmet need and represents a first-to-market opportunity with no approved treatments

EEAS, US patients. * Significance level P < 0.1, ** P < 0.05, *** P < 0.01.

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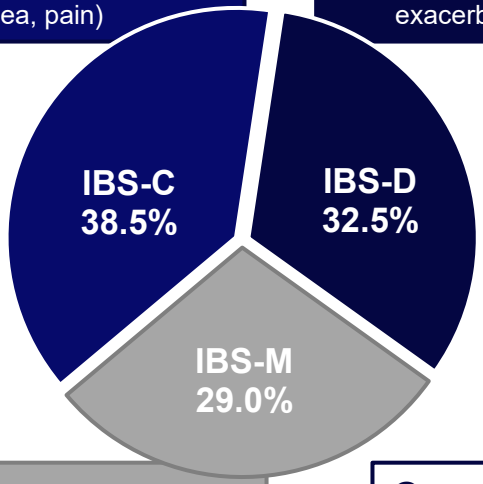
IBS IS A SIGNIFICANT MARKET AND OPPORTUNITY

IBS-C

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

IBS-D

- Estimated **~1.4 mn** US cases treated in 2019
- Leading IBS-D therapeutic - rifaximin - antibiotic potentially exacerbates underlying microbiome etiology



IBS-M

- Significant commercial opportunity
- No approved therapeutic regime
- Fluctuating symptoms require single treatment

Current Market IBS-C and IBS-D

- **10-15%** estimated incidence in US & Europe
- **60-70%** of diagnosed IBS patients are female
- **$2.4 bn** projected US market by 2024

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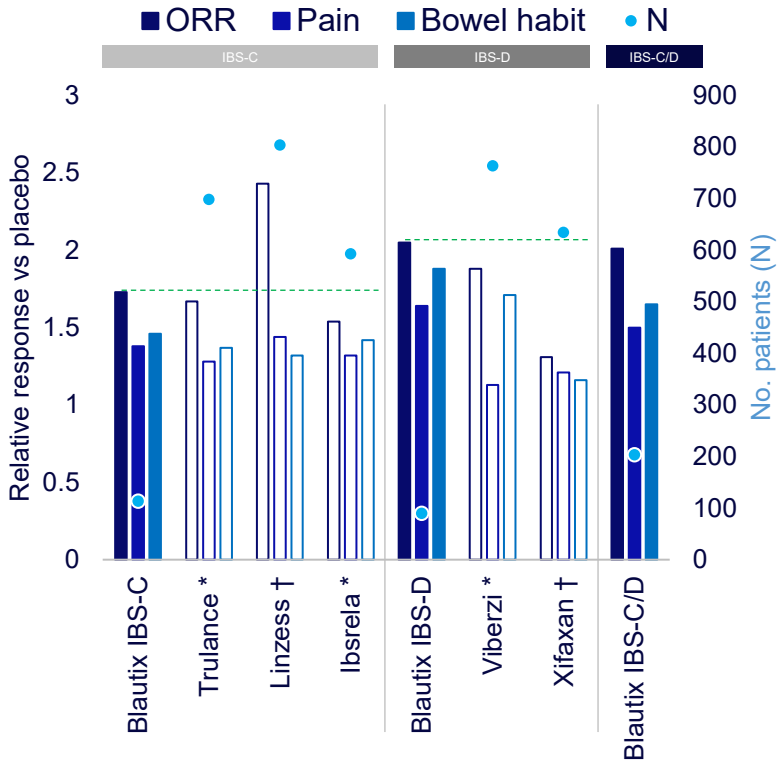
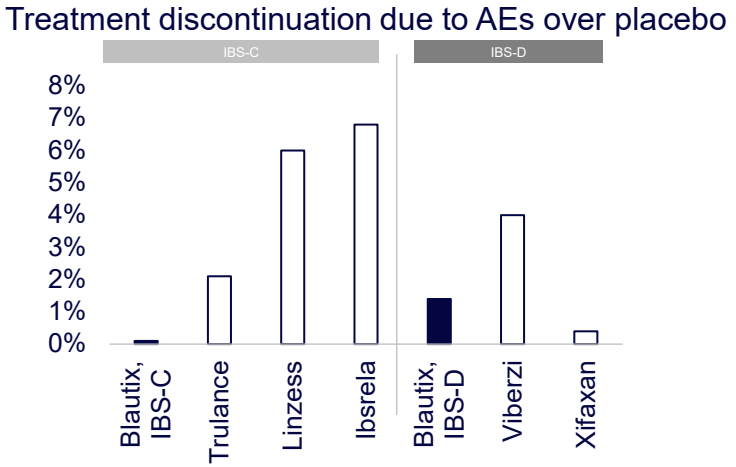
BLAUTIX® COMPARABLE TO APPROVED IBS THERAPEUTICS

- Blautix Phase II relative response rates are competitive with approved IBS drugs
- Effects on bowel habit and abdominal pain also comparable to approved drugs for IBS-C *or* IBS-D
- Uniquely, Blautix is the only therapeutic to do so in both IBS-C *and* IBS-D
- Blautix has an attractive safety and tolerability profile compared to current treatment options





- Diarrhea is a common side effect of current IBS-C drugs. 20% patients receiving Linzess experience diarrhea; 2.5%, 2% and 1% receiving Ibsrela, Linzess and Trulance, respectively, have *severe* diarrhea
- Linzess, Trulance and Ibsrela FDA approvals have black box warnings for severe dehydration
- Viberzi associated with risk of pancreatitis
- Other IBS-D products such as serotonin 5-HT_3 antagonists commonly associated with constipation (e.g. Lotronex, up to 29%)
- Off-label mu-opiod receptor antagonists and antidepressants can be associated with cardiac AEs

Blautix Phase II US EEAS. Data for approved products best of two registration studies (FDA label). [1] Viberzi bowel habit endpoint - reduction in BSS to <5 on >50% of days in 12 weeks of treatment. † Enrolled patients based on Rome II criteria; * Enrolled patients based on Rome III criteria

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BLAUTIX® FUTURE DEVELOPMENT

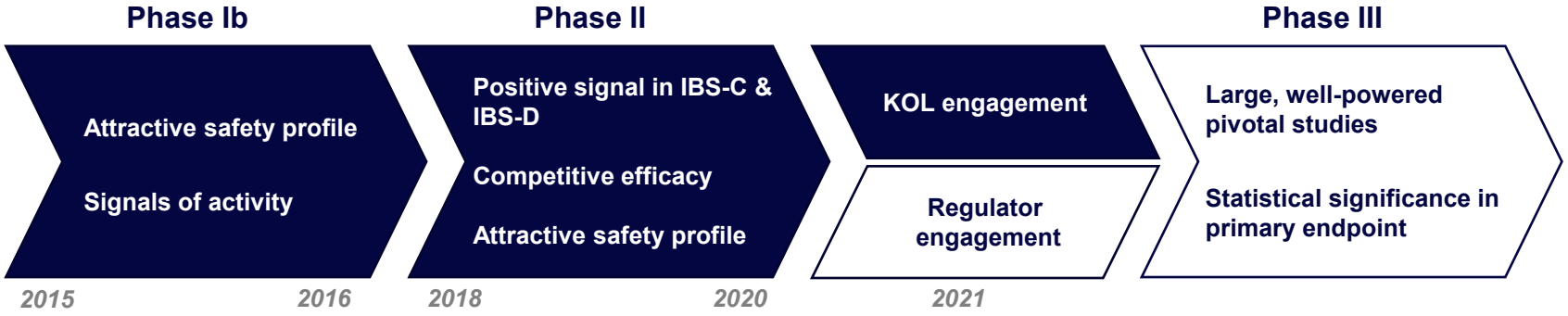
Signal finding Phase II presents multiple options and opportunities for further development

Positive signal in IBS-C and IBS-D supports development in multiple indications:

- IBS-D
- IBS-C
- IBS-M

Phase II data and regulatory guidelines provide options for pivotal endpoints:

- Overall responder rate
- Bowel habit



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