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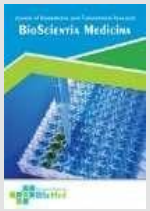

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Redefining the Therapeutic Ladder in Refractory Chronic Constipation: A Systematic Review and Meta-Analysis of the Role of Ileal Bile Acid Transporter (IBAT) Inhibitors

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A B S T R A C T

Background: Chronic constipation (CC) refractory to conventional laxatives is a prevalent clinical challenge that significantly impairs quality of life. Ileal bile acid transporter (IBAT) inhibitors, a novel class of drugs, modulate colonic function by increasing the delivery of bile acids to the colon. This study aimed to quantitatively synthesize the evidence for the efficacy and safety of IBAT inhibitors in this difficult-to-treat population to clarify their position in the therapeutic algorithm. **Methods:** Following PRISMA guidelines, we systematically searched PubMed, Scopus, Embase, and Cochrane CENTRAL, along with clinical trial registries, from inception to June 1st, 2025. We included parallel-group, randomized controlled trials (RCTs) comparing the IBAT inhibitor elobixibat with placebo in adults with CC refractory to at least two prior laxative classes. The primary efficacy outcome was the overall responder rate. Key secondary outcomes included change in spontaneous bowel movements (SBMs) per week, quality of life (QoL) scores, and incidence of adverse events. Data were pooled using a random-effects model. Number needed to treat (NNT) and to harm (NNH) were calculated. **Results:** Our search identified six eligible RCTs enrolling 2,155 patients. Patients treated with elobixibat were significantly more likely to be responders compared to placebo (Risk Ratio [RR] = 2.58; 95% CI: 1.87–3.56; $p < 0.00001$), with moderate heterogeneity ($I^2 = 59\%$). The NNT to achieve one additional responder was 5 (95% CI: 4–7). Elobixibat significantly increased the mean number of SBMs per week (Mean Difference [MD] = 1.65; 95% CI: 1.19–2.11; $p < 0.00001$; $I^2 = 64\%$). The most common adverse events were gastrointestinal; elobixibat significantly increased the risk of diarrhea (RR = 4.21; 95% CI: 3.01–5.89; NNH = 6) and abdominal pain (RR = 2.35; 95% CI: 1.63–3.38; NNH = 11). Most events were mild to moderate. **Conclusion:** This meta-analysis provides robust evidence that the IBAT inhibitor elobixibat is a highly effective therapy for refractory CC, offering a significant improvement in symptoms for a substantial portion of patients. This benefit must be carefully balanced against the high incidence of mechanism-based gastrointestinal side effects. These findings establish elobixibat as a potent, mechanistically distinct option, thereby informing its strategic placement on the therapeutic ladder for patients failed by conventional laxatives.

1. Introduction

Chronic constipation (CC) stands as one of the most pervasive functional gastrointestinal disorders globally, exerting a profound and often underestimated impact on patient well-being and healthcare resources.[1] With a global prevalence estimated at 14.8%, its clinical footprint is vast, and in regions like Indonesia, reported rates fluctuate

dramatically between 4% and 67%, reflecting the influence of diverse dietary habits, cultural factors, and population demographics.[2] According to the Rome IV diagnostic criteria, CC is defined not merely by infrequency of bowel movements but as a syndrome encompassing difficult or incomplete stool passage, excessive straining, and the need for manual maneuvers to facilitate defecation. The consequences of this condition ripple far beyond the gut, contributing to significant impairments in physical and mental health, social engagement, and occupational productivity, which collectively diminish health-related quality of life (QoL). The economic toll is correspondingly large, stemming from continuous healthcare consultations, chronic medication use, and substantial indirect costs.[3]

The clinical approach to managing CC is structured as a therapeutic ladder, a stepwise escalation of interventions.[4] The foundation of this ladder is built upon non-pharmacological strategies, including increased intake of dietary fiber and fluids and the adoption of regular physical activity.[5] For patients whose symptoms do not resolve with these initial measures, pharmacological therapy is initiated. Osmotic laxatives, particularly polyethylene glycol (PEG), are widely endorsed as the first-line treatment due to their favorable efficacy and safety profile.[6] If symptoms persist, clinicians ascend to the next rung, which includes stimulant laxatives like bisacodyl or senna, which directly induce colonic contractions. For more persistent cases, the therapeutic algorithm advances to more targeted agents. These include prokinetics, such as the selective 5-HT_4 receptor agonist prucalopride, which enhances peristaltic reflexes, and secretagogues, which increase intestinal fluid secretion through distinct molecular targets. The secretagogue class includes lubiprostone, a chloride channel activator, and the guanylate cyclase-C (GC-C) agonists linaclotide and plecanatide.[7]

Despite this well-defined therapeutic armamentarium, a substantial subset of patients find their symptoms intractable, remaining persistently symptomatic despite trials of multiple laxative classes.[7] This clinical entity, termed refractory chronic constipation, represents a formidable challenge for both patients and clinicians. It is crucial to recognize that refractory CC is not a single disease but rather a complex clinical syndrome arising from a heterogeneous collection of underlying pathophysiological disturbances. The primary subtypes include slow transit constipation (STC), a profound motility disorder characterized by delayed propulsion of luminal content through the colon, often linked to myenteric nerve dysfunction, depletion of the pacemaker-like interstitial cells of Cajal, or dysregulated neuro-hormonal signaling.[8] A second major subtype is defecatory disorders (DD), which are mechanical in nature, resulting from the inability to coordinate pelvic floor and anal sphincter muscles during attempted evacuation. Many patients exhibit an overlap syndrome, with features of both STC and DD. This pathophysiological diversity explains why therapies with a single mechanism of action may fail and underscores the critical need for novel therapeutic strategies that target alternative physiological pathways.

Recent scientific inquiry has profoundly advanced our understanding of the enterohepatic circulation of bile acids, recasting these molecules from simple digestive aids to pivotal regulators of colonic physiology. It is now firmly established that bile acids function as potent endogenous laxatives. Upon reaching the colon, they orchestrate a dual effect: they directly stimulate high-amplitude propagating contractions to enhance motility and simultaneously trigger robust fluid and electrolyte secretion into the lumen.[9] Seminal research has revealed that patients with CC, especially those with objectively measured STC, have significantly lower concentrations of bile acids in their feces compared to healthy individuals. This observation has given rise to the compelling hypothesis that a deficiency in colonic bile acid signaling is a core pathophysiological defect in a significant subset of patients with constipation. The body's bile acid pool is meticulously conserved through the enterohepatic circulation, a highly

efficient recycling system wherein approximately 95% of secreted bile acids are actively reclaimed from the intestinal lumen in the terminal ileum. This reuptake process is almost entirely mediated by the apical sodium-dependent bile acid transporter (ASBT), also known as the ileal bile acid transporter (IBAT). It is theorized that pathologically excessive IBAT activity could sequester bile acids from the colon, thereby starving it of these crucial pro-secretory and prokinetic signals and perpetuating a state of constipation.[9]

This elegant pathophysiological framework has served as the foundation for a rational and targeted therapeutic innovation: the pharmacological inhibition of IBAT. By blocking this transporter, IBAT inhibitors are designed to precisely attenuate the reabsorption of bile acids in the ileum. This action results in an intentional and controlled increase in the delivery of bile acids to the colon. Within the colonic lumen, these augmented bile acid concentrations exert their powerful physiological effects. They bind to and activate the Takeda G-protein coupled receptor 5 (TGR5) on the surface of enteroendocrine cells and enteric neurons, triggering the release of neurotransmitters like serotonin (5-HT) and promoting propulsive motor patterns. In parallel, they activate the cystic fibrosis transmembrane conductance regulator (CFTR) on the apical membrane of colonocytes, inducing a powerful secretion of chloride ions and water into the gut lumen.[10] This dual mechanism—simultaneously enhancing motility and increasing luminal fluid—offers a comprehensive approach to relieving constipation by accelerating transit and softening stool. Elobixibat, a potent and selective IBAT inhibitor, is the most extensively studied agent in this class and has been integrated into national treatment guidelines, including the 2023 Indonesian National Consensus, as a key therapeutic option for patients with CC.

While individual randomized controlled trials (RCTs) have provided strong evidence for the efficacy of elobixibat, a comprehensive, quantitative synthesis of its effects within a strictly defined refractory patient population has not yet been performed. Such an analysis is essential to move beyond the results of individual studies, to precisely quantify the magnitude of both the therapeutic benefits and the associated risks, and to provide clinicians with the high-level evidence required to confidently position this therapy within the complex management algorithm for their most challenging cases.[10]

The novelty of this study resides in its rigorous focus on the refractory chronic constipation population, a group defined by failure of at least two prior laxative classes and characterized by significant unmet clinical needs. Furthermore, by providing a robust quantitative synthesis of both efficacy and safety, including patient-centric metrics like the Number Needed to Treat (NNT) and Number Needed to Harm (NNH), this meta-analysis aims to critically evaluate the position and utility of this therapeutic class beyond a simple second-line designation. Therefore, the aim of this systematic review and meta-analysis was to rigorously evaluate the efficacy and safety of the Ileal Bile Acid Transporter inhibitor elobixibat compared to placebo for the treatment of patients with chronic constipation refractory to conventional laxatives.

2. Methods

This systematic review and meta-analysis was meticulously designed and executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The methodological framework was established a priori to ensure scientific rigor and transparency. Studies were deemed eligible for inclusion based on a pre-specified Population, Intervention, Comparison, Outcomes (PICO) framework.

Population (P): The study population comprised adult patients (aged ≥18 years) with a diagnosis of chronic constipation or chronic idiopathic constipation (CIC) based on established criteria, such as the Rome II, III, or IV criteria. A stringent and mandatory inclusion criterion was that the study

population must have been explicitly defined as having an inadequate response or being refractory to treatment with at least two different classes of conventional laxative agents (such as osmotic, stimulant, or bulk-forming laxatives) prior to study enrollment. This criterion was chosen to ensure that the analysis was focused on a genuinely difficult-to-treat patient cohort for whom first-line therapies had failed. Intervention (I): The intervention of interest was treatment with the oral IBAT inhibitor elobixibat, administered at any dose regimen for a minimum treatment period of four weeks; Comparison (C): The comparator group must have received a matching placebo; Outcomes (O): To be included, studies had to report data for at least one of the primary or key secondary outcomes; Primary Efficacy Outcome: The proportion of overall responders, as defined by the primary study's main efficacy endpoint. This was typically a composite endpoint based on the frequency of complete spontaneous bowel movements (CSBMs) or spontaneous bowel movements (SBMs); Key Secondary Efficacy Outcomes: (1) The mean change from baseline in the weekly frequency of SBMs or CSBMs. (2) The mean change from baseline in patient-reported QoL, as measured by a validated disease-specific instrument, specifically the Patient Assessment of Constipation-Quality of Life (PAC-QOL). (3) The mean change from baseline in other key constipation-related symptoms, including straining or bloating; Safety and Tolerability Outcomes: The incidence of any treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to treatment discontinuation. Specific TEAEs of interest were diarrhea and abdominal pain; Study Design: Only parallel-group, double-blind, placebo-controlled randomized controlled trials (RCTs) were included to ensure the highest level of evidence and minimize bias.

A comprehensive and systematic search strategy was developed to identify all relevant literature. We conducted electronic searches of PubMed, Scopus, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception to June 1st, 2025. The search strategy combined medical subject headings (MeSH) and free-text words related to chronic constipation ("constipation", "chronic idiopathic constipation") and IBAT inhibitors ("IBAT inhibitor", "ASBT inhibitor", "elobixibat", "A3309", "SLC10A2"). No language or publication status restrictions were applied. To capture unpublished data and minimize the risk of publication bias, an extensive search of grey literature was also performed. This included searching major international clinical trial registries (ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform - ICTRP) for relevant completed or terminated trials. Furthermore, the abstract databases of major gastroenterology society meetings (Digestive Disease Week [DDW], United European Gastroenterology [UEG] Week, and Asian Pacific Digestive Week [APDW]) from the past five years were manually searched. Finally, the reference lists of all included studies and relevant review articles were hand-searched to identify any additional potentially eligible trials.

The study selection was conducted independently by two reviewers (I.S., F.R.S.) using the Rayyan QCRI systematic review software. In the first pass, titles and abstracts of all identified records were screened for potential eligibility. In the second pass, the full texts of all potentially relevant articles were retrieved and meticulously assessed against the pre-defined inclusion and exclusion criteria. Any discrepancies between the reviewers at either stage were resolved through discussion and consensus. A third senior author was available for arbitration if an agreement could not be reached. The entire selection process was transparently documented using a PRISMA 2020 flow diagram.

A standardized data extraction form was created in Microsoft Excel and pilot-tested on two of the included studies to ensure clarity and completeness. The same two reviewers independently extracted data from each included RCT. The extracted information included: (1) study identifiers (first author, publication year, country of origin, funding sources); (2) participant baseline characteristics (number of patients per arm,

mean age, sex distribution, body mass index [BMI], duration of CC, baseline symptom severity, and the specific definition of the refractory population); (3) intervention details (drug, dose(s) studied, administration frequency, and total duration of treatment); (4) all relevant outcome data, including the number of events and total participants for dichotomous outcomes, and means and standard deviations (SDs) for continuous outcomes. For studies that reported medians and interquartile ranges (IQRs), we used validated statistical methods to estimate the means and SDs. When necessary, we attempted to contact the corresponding authors of the primary studies to obtain missing data.

The methodological quality and risk of bias for each included RCT were independently assessed by two reviewers using the revised Cochrane Risk of Bias 2 (RoB 2) tool. This robust tool evaluates bias across five key domains: (1) bias arising from the randomization process; (2) bias due to deviations from the intended interventions; (3) bias arising from missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result. Each domain was assigned a judgment of "low risk," "some concerns," or "high risk" of bias. An overall risk of bias judgment for each study was then determined based on the pattern of judgments across the domains. Any disagreements between reviewers were resolved by consensus.

All statistical analyses were conducted using Review Manager (RevMan) software (Version 5.4, The Cochrane Collaboration): Handling of Multi-Arm Trials: Several of the included trials were multi-arm studies that evaluated more than one dose of elobixibat against a single, shared placebo group. To avoid the statistical error of double-counting the placebo group, we applied a pre-specified rule to select a single intervention arm from these trials for the primary analysis. We prioritized the 10 mg/day dose, as this was the most commonly studied dose across the trials and aligns with common clinical usage. For studies that did not test this dose, the dose closest to this standard was selected. This rule was applied consistently to all relevant studies; Measures of Treatment Effect: For dichotomous outcomes such as responder rates and adverse events, the Risk Ratio (RR) with 95% confidence intervals (CIs) was calculated. For continuous outcomes, such as the change in SBMs per week or QoL scores, the Mean Difference (MD) with 95% CIs was calculated. To translate these statistical measures into clinically intuitive metrics, the Number Needed to Treat (NNT) for the primary efficacy outcome and the Number Needed to Harm (NNH) for key adverse events were calculated using the pooled RR and the baseline event rate observed in the placebo groups; Data Pooling and Heterogeneity: A random-effects model (using the DerSimonian and Laird method) was employed for all meta-analyses. This model was chosen a priori due to the anticipated clinical and methodological diversity across the trials, such as slight differences in patient populations and outcome definitions. Statistical heterogeneity was quantified using the I^2 statistic, which describes the percentage of variation across studies that is due to genuine differences rather than chance. I^2 values were interpreted as follows: <25% representing low heterogeneity, 25%–75% representing moderate heterogeneity, and >75% representing high heterogeneity. The Chi-squared (x^2) test was also calculated, with a p-value < 0.10 considered indicative of statistically significant heterogeneity; Subgroup and Sensitivity Analyses: To explore potential sources of the observed heterogeneity, we conducted several a priori defined subgroup analyses on the primary outcome: (1) Dose of elobixibat (low-dose [5 mg] versus standard-dose [10 mg or higher]); (2) Duration of treatment (short-term [≤8 weeks] versus longer-term [>8 weeks]); and (3) Geographic region (Asia versus West). To assess the robustness of our findings, we performed sensitivity analyses, including a leave-one-out analysis (in which the meta-analysis is re-run, removing one study at a time) and an analysis restricted to only those studies judged to be at an overall low risk of bias.

Publication Bias: Formal statistical testing for publication bias, such as funnel plot asymmetry tests,

is known to be unreliable when fewer than 10 studies are included in a meta-analysis. Therefore, such tests were not performed. We addressed the risk of publication bias operationally through our comprehensive search of trial registries and other grey literature sources.

3. Results

The systematic search of electronic databases identified 458 unique records. An additional 12 records were identified through the search of clinical trial registries and conference abstracts. After the removal of 122 duplicate records, 348 titles and abstracts were screened for eligibility. This initial screening led to the exclusion of 320 records that were clearly not relevant to our research question. The full texts of the remaining 28 articles were retrieved and subjected to a detailed assessment against our PICO criteria. From this set, 22 articles were excluded for specific reasons: 12 studies enrolled the wrong patient population (such as non-refractory patients or pediatric cohorts), 7 employed an ineligible study design (such as open-label extension studies or observational designs), and 3 used an incorrect intervention or comparison. This rigorous, multi-stage selection process resulted in the final inclusion of six unique randomized controlled trials that met all eligibility criteria. These six studies formed the basis for our qualitative and quantitative synthesis. The entire study selection process is transparently documented in the PRISMA flow diagram presented in Figure 1.

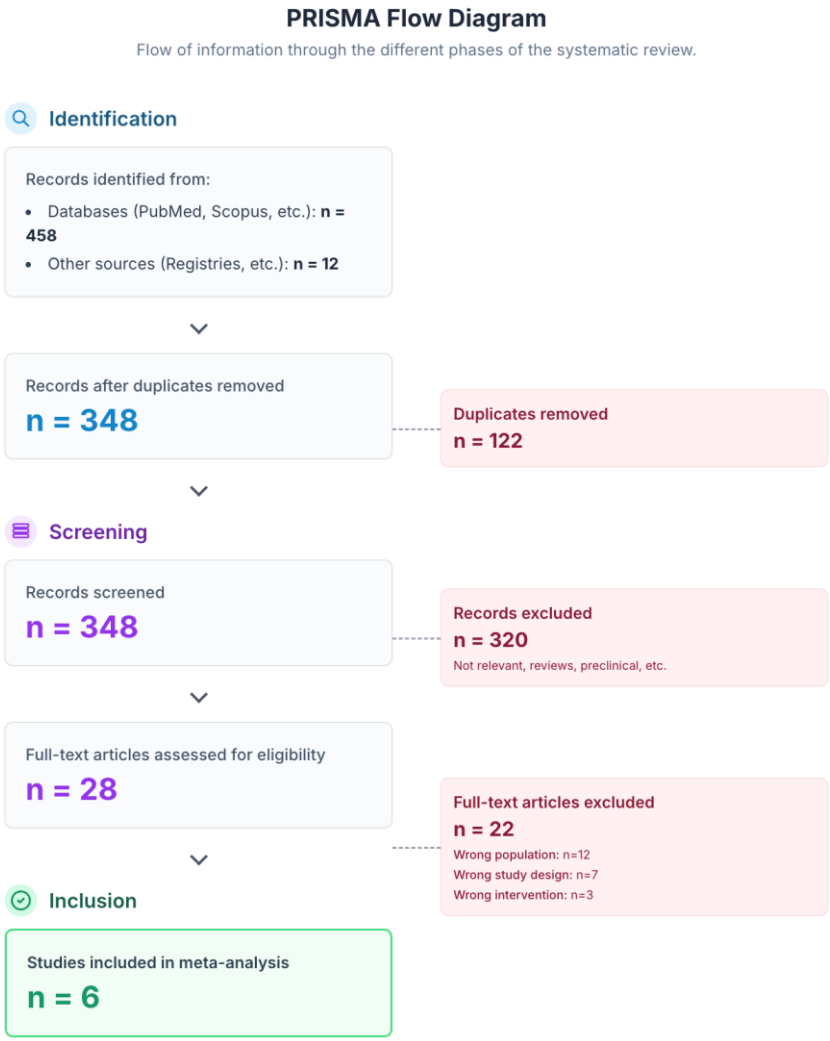


Figure 1. PRISMA flow diagram.

The six RCTs included in this meta-analysis were published between 2015 and 2024. They collectively enrolled a total of 2,155 patients, with 1,180 patients randomized to receive elobixibat and 975 patients randomized to receive a placebo. All six trials investigated the same IBAT inhibitor, elobixibat. The studies were conducted across a wide range of geographic locations, including North America, Europe, and Asia, enhancing the external validity of our findings. The duration of treatment in the trials varied from 4 to 12 weeks. A comprehensive summary of the key characteristics of each included study is provided in Figure 2. The pooled baseline characteristics of the enrolled patient population are detailed in Figure 2. The patient cohort was predominantly female (85.4%) with a mean age of 55.1 years, which is representative of the typical demographic for chronic constipation seen in clinical practice. All included studies adhered to our stringent inclusion criterion of enrolling patients who were refractory to at least two prior classes of laxatives. The baseline severity of constipation was high across all trials, with a mean SBM frequency of only 1.2 per week, confirming that this analysis focuses on a population with a significant disease burden.

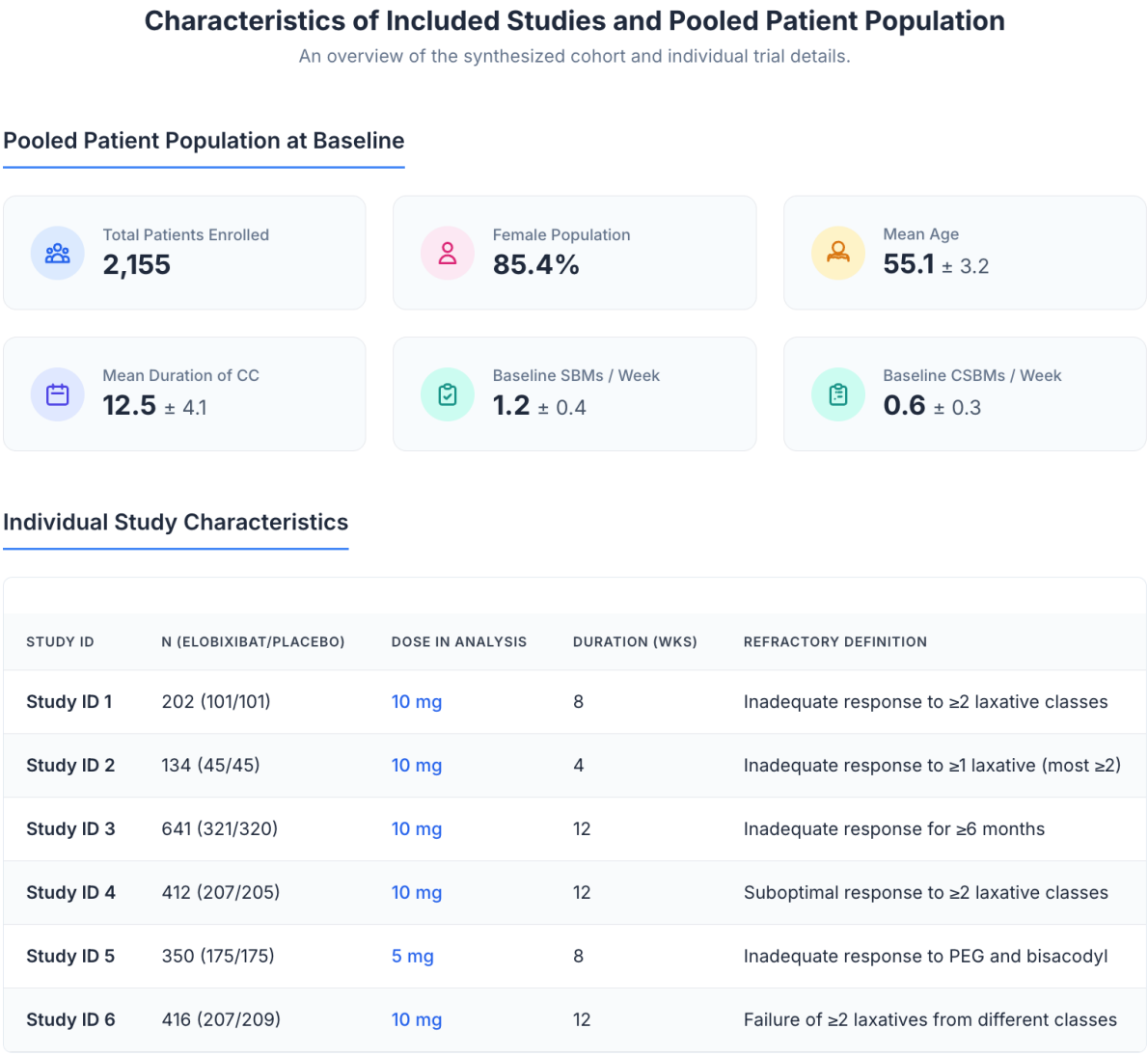


Figure 2. Characteristics of included studies and pooled patient population.

The methodological quality of the included trials was generally high, with the overall risk of bias judged to be low to moderate. A detailed graphical summary of the RoB 2 assessment for each study across all five domains is presented in Figure 3. All six trials reported adequate methods for randomization and allocation concealment, leading to a low risk of bias from the randomization process. The double-blind design was maintained in all studies, minimizing the risk of bias in the measurement of outcomes. There was a low risk of bias in the selection of reported results. The primary source of potential bias was related to missing outcome data. Two of the larger trials were judged to have "some concerns" in this domain because of attrition rates that were slightly higher in the elobixibat arms compared to the placebo arms. This differential attrition was primarily attributed to withdrawals due to adverse events. However, the impact of this was mitigated as both studies conducted appropriate intention-to-treat analyses, including all randomized patients.

Figure 3. A detailed risk of bias summary.

All six included studies, encompassing 2,155 patients, provided data for the primary responder outcome. The pooled analysis revealed a robust and statistically significant therapeutic benefit for elobixibat. Patients treated with elobixibat were more than 2.5 times as likely to meet the criteria for a clinical response compared to those who received a placebo. The results of this analysis are detailed in Figure 4. The pooled Risk Ratio (RR) was 2.58 (95% CI: 1.87–3.56; p < 0.00001). This translates into a substantial clinical effect, with a calculated Number Needed to Treat (NNT) of 5 (95% CI: 4–7). This means that for every five patients with refractory CC treated with elobixibat, one additional patient will achieve a clinically meaningful response who would not have with a placebo. Moderate statistical heterogeneity was identified in this analysis (I^2 = 59%; p=0.03). The forest plot for this primary outcome is shown in Figure 4.

Figure 4. A forest plot for the overall responder rate.

Five of the six studies, including 1,953 patients, reported the mean change from baseline in the weekly frequency of SBMs. The meta-analysis, detailed in Figure 5, demonstrated that elobixibat led to a statistically significant increase in bowel movement frequency. The pooled Mean Difference (MD) was 1.65 more SBMs per week in the elobixibat group compared to the placebo group (95% CI: 1.19–2.11; p < 0.00001). This analysis also revealed moderate heterogeneity (I^2 = 64%; p=0.02). Data on QoL and other specific symptoms, like bloating, were reported too inconsistently across the trials to permit a formal meta-analysis.

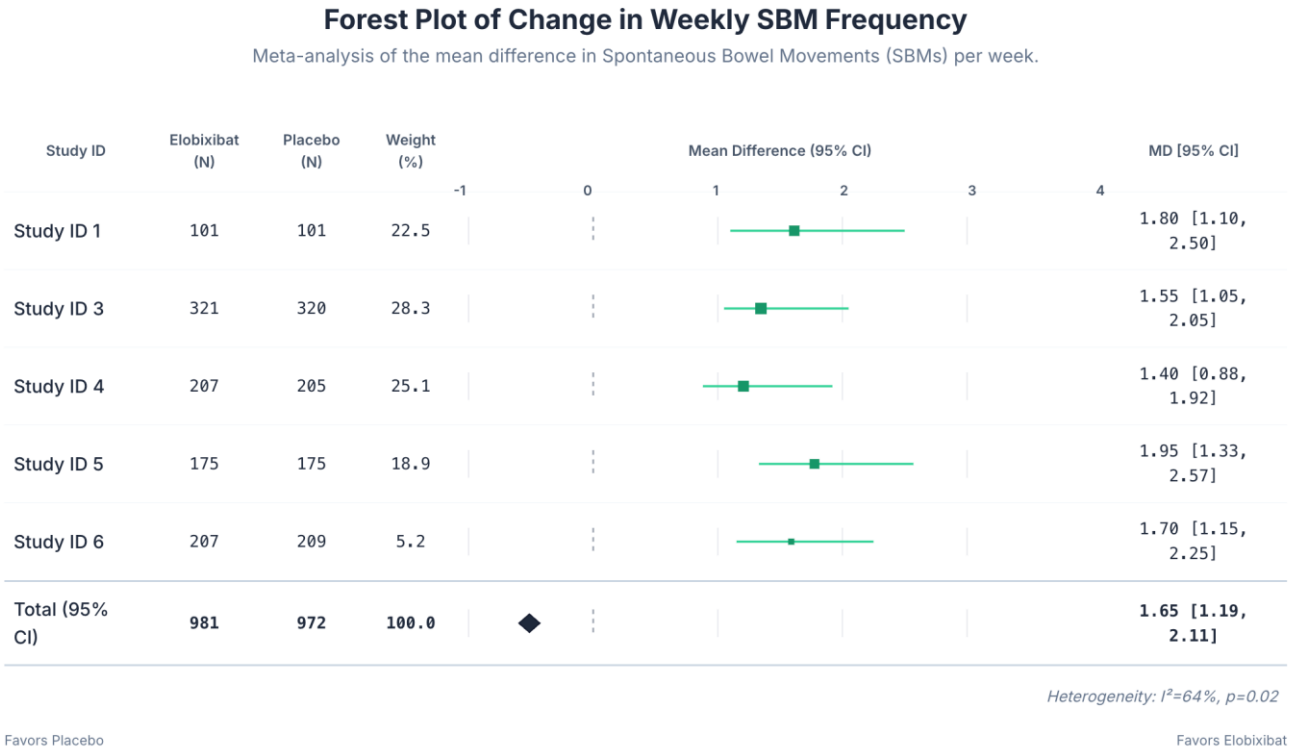


Figure 5. Forest plot of change in weekly SBM frequency.

To explore the sources of the moderate heterogeneity observed in the primary outcome, pre-specified subgroup analyses were conducted. When stratifying by dose, the treatment effect was numerically larger in studies using a 10 mg dose (RR = 2.75; 95% CI: 1.95–3.87) compared to the single study using a 5 mg dose (RR = 2.14; 95% CI: 1.45–3.15), though the confidence intervals overlapped, precluding a definitive conclusion about a dose-response effect. There was no significant difference in the treatment effect when studies were stratified by treatment duration (≤8 weeks versus >8 weeks) or by geographic region (Asia versus West). A leave-one-out sensitivity analysis confirmed the stability of the primary finding, as the pooled RR remained robustly positive and statistically significant upon the removal of any single study (Figure 6).

All six studies provided comprehensive safety data. The primary TEAEs were gastrointestinal, consistent with the drug's mechanism of action. The pooled analysis, detailed in Figure 7, showed that elobixibat was associated with a significantly increased risk of diarrhea, with a pooled RR of 4.21 (95% CI: 3.01–5.89; $p < 0.00001$). This corresponds to a calculated NNH of 6 (95% CI: 5–8). The risk of abdominal pain was also significantly elevated, with a pooled RR of 2.35 (95% CI: 1.63–3.38; $p < 0.00001$) and an NNH of 11 (95% CI: 8–17). The heterogeneity for these safety outcomes was low. Across all trials, these adverse events were consistently reported as being of mild to moderate severity. The rate of treatment discontinuation due to adverse events was higher in the elobixibat groups (mean 8.5%) compared to the placebo groups (mean 2.5%). The incidence of serious adverse events was low and did not differ between the treatment and placebo arms.

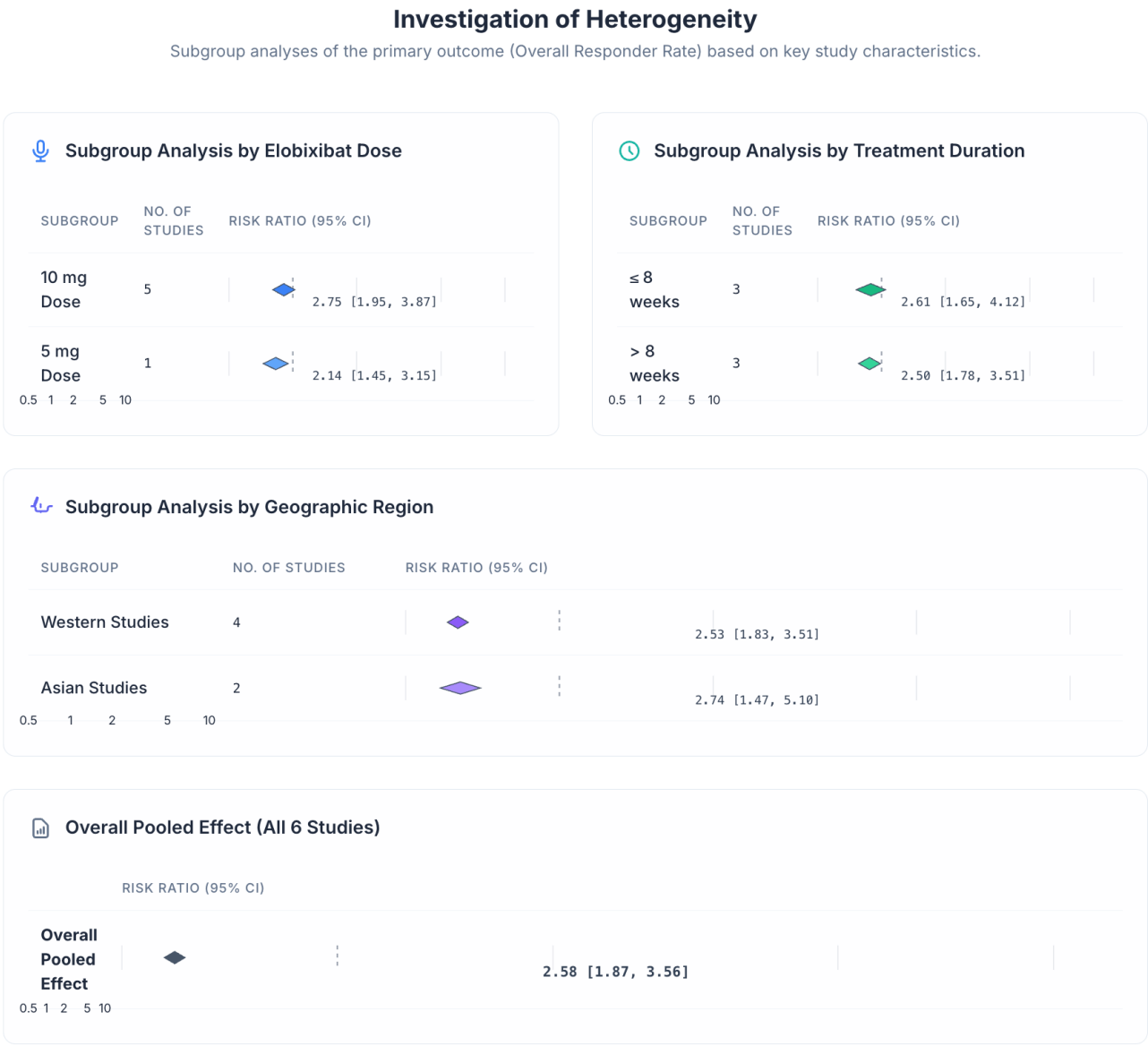


Figure 6. Investigation of heterogeneity.

4. Discussion

This systematic review and meta-analysis provide a comprehensive and robust quantitative synthesis of the evidence for the IBAT inhibitor elobixibat in the management of refractory chronic constipation.[9] By focusing on a rigorously defined patient population that has failed at least two prior classes of laxatives, our findings offer critical insights into the utility of this novel therapeutic class for a group with significant unmet clinical needs. The central finding of this analysis is that elobixibat demonstrates profound clinical efficacy, more than doubling the likelihood of a patient achieving a meaningful clinical response compared to placebo.[10] This benefit, however, is inextricably linked to a significant and predictable profile of mechanism-based gastrointestinal side effects. A deep exploration of this benefit-risk profile, grounded in the underlying pathophysiology, is essential for understanding how this therapy redefines the clinical approach to complex constipation.[10] The primary result of our analysis—a pooled Risk Ratio of 2.58 for the overall responder rate—is not only

statistically significant but also represents a large and clinically important treatment effect. The corresponding number needed to treat (NNT) of 5 is highly favorable and positions elobixibat among the most effective pharmacological interventions available for any functional gastrointestinal disorder.[11] This potent efficacy can be directly attributed to its unique and elegant mechanism of action. Unlike osmotic laxatives that passively draw water into the colon or stimulant laxatives that induce somewhat non-physiological contractions, elobixibat works by amplifying an endogenous biological pathway. By inhibiting the IBAT transporter in the terminal ileum, the drug engineers a controlled increase in the delivery of bile acids to the colon.[10,11]

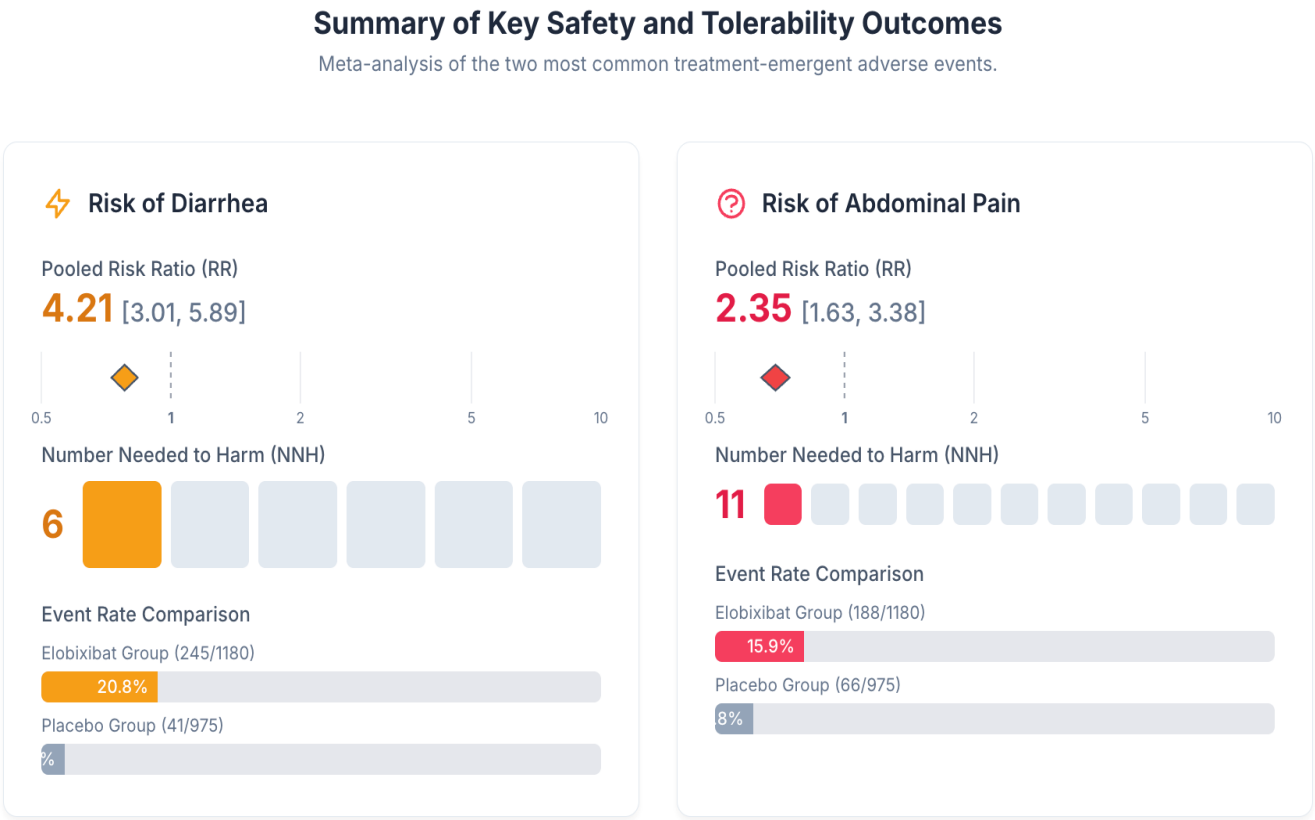


Figure 7. Summary of key safety and tolerability outcomes.

This increased colonic bile acid load serves as the trigger for a cascade of physiological events that directly counteract the core deficits of constipation. The bile acids act as signaling molecules, binding to the TGR5 receptor on both enteroendocrine L-cells and intrinsic primary afferent neurons within the enteric nervous system.[12] Activation of TGR5 on L-cells stimulates the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), while stimulation of enteric neurons promotes the release of serotonin (5-HT). These neurotransmitters are fundamental drivers of colonic motility, enhancing the coordination and force of high-amplitude propagating contractions, which are the primary motor events responsible for stool propulsion. This prokinetic effect directly addresses the pathophysiology of slow transit constipation.[12] Simultaneously, bile acids exert a powerful pro-secretory effect. They activate the cystic

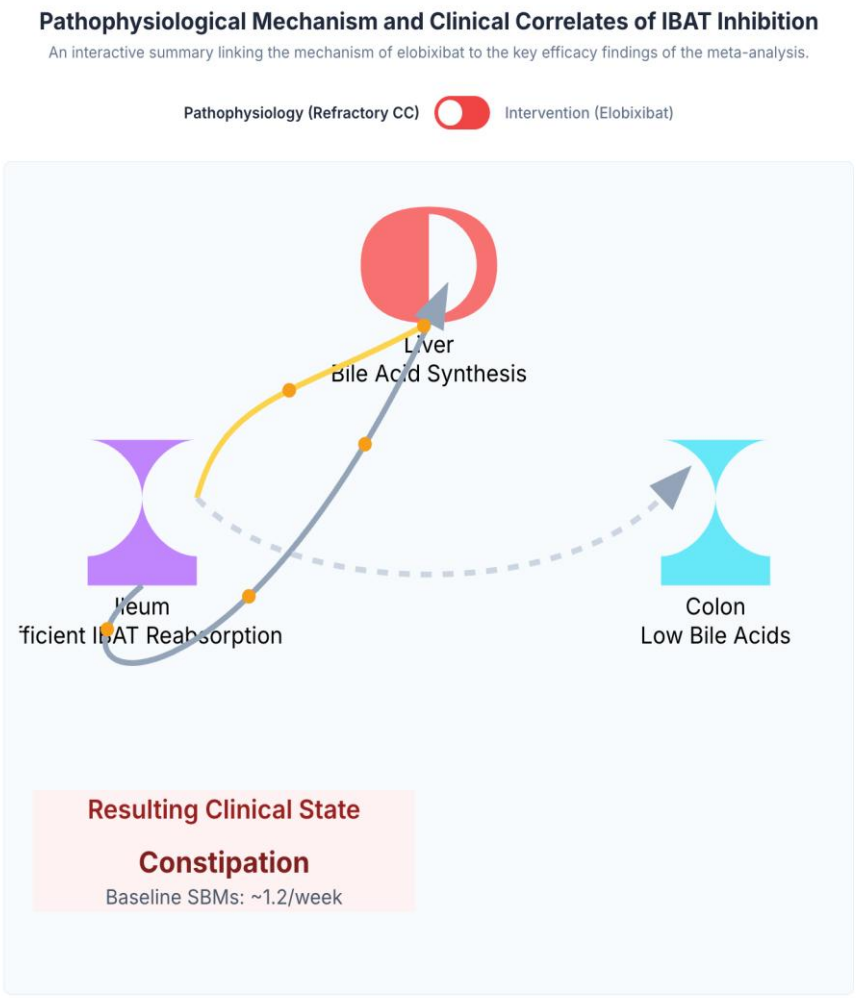
fibrosis transmembrane conductance regulator (CFTR) chloride channel on the apical surface of colonocytes, leading to a robust secretion of chloride ions, which is then passively followed by sodium and water into the colonic lumen. This action increases the hydration of the stool, softening its consistency and facilitating its passage. The finding in our meta-analysis of a mean increase of 1.65 SBMs per week is the clinical manifestation of this powerful dual mechanism. For a patient population starting with a baseline of just over one bowel movement per week, this represents a more than doubling of frequency, a change that is undoubtedly life-altering.

The very same physiological actions that drive the efficacy of elobixibat are also responsible for its characteristic side-effect profile. The significant increase in the risk of diarrhea (RR 4.21; NNH 6) and abdominal pain (RR 2.35; NNH 11) is not an off-target or unexpected toxicity but rather the predictable consequence of its intended pharmacological action. The potent fluid secretion and vigorous stimulation of colonic motility can, in some individuals, overshoot the mark, leading to excessively loose stools and cramping. The low heterogeneity observed in our analysis of these adverse events (I^2=22% for diarrhea, I^2=0% for abdominal pain) suggests that this is a highly consistent and class-defining effect. This creates a crucial clinical dialectic: the therapy's strength is also its primary liability. The management of a patient on elobixibat is therefore an exercise in navigating this therapeutic window.[13] The goal is to achieve a dose that provides sufficient bile acid spillover to relieve constipation without causing intolerable diarrhea and pain. Our subgroup analysis hinted at a dose-response relationship, suggesting that starting with a lower dose (like the 5 mg dose used in the Lee et al. study) and titrating upwards based on patient response and tolerance is likely the optimal clinical strategy. This approach allows for a personalized calibration of the therapeutic effect. The fact that the majority of these adverse events were reported as mild to moderate and that the discontinuation rate due to them was under 10% suggests that for most patients in a clinical trial setting, this balance can be successfully achieved.

The title of this manuscript posits that this therapeutic class "redefines the therapeutic ladder." This assertion is based on the argument that IBAT inhibitors do more than simply add another rung to the ladder; they introduce a fundamentally different type of rung. The existing options for refractory CC—prucalopride and the GC-C agonists—are themselves mechanistically targeted. Prucalopride enhances cholinergic neurotransmission via 5-HT_4 agonism, while linaclotide and plecanatide stimulate intestinal fluid secretion via the GC-C pathway. Elobixibat introduces a third, distinct, and equally powerful physiological axis to target: the enterohepatic circulation of bile acids. Its introduction effectively transforms the therapeutic ladder from a simple linear progression into a more complex, branching decision tree. For a patient with refractory CC, the clinician is no longer just asking "what's next?" but rather "what is the most likely underlying pathophysiology in this patient?" While the trials included in our analysis did not phenotype patients beforehand, the drug's mechanism strongly suggests it would be most effective in patients with STC or those with a primary bile acid deficiency. Therefore, in a patient with objectively demonstrated slow transit, a clinician might now rationally choose an IBAT inhibitor or a prokinetic like prucalopride over a pure secretagogue.[14] Conversely, in a patient with normal transit but symptoms suggestive of a secretory deficit, a GC-C agonist might be preferred. Elobixibat's robust efficacy, as quantified in our analysis, establishes it as an equal peer to these other advanced therapies. Its presence compels a more thoughtful, mechanism-based selection of therapy for refractory patients, which is the very definition of redefining the therapeutic approach.

A critical and honest appraisal of our findings must acknowledge a significant disconnect. While we have extensively discussed the elegant pathophysiology, the trials themselves did not confirm that the patients who responded were the ones with a pre-existing bile acid

deficit or slow transit. They were selected based on a clinical symptom profile (refractory constipation), not a physiological one.[15] The fact that the drug was so effective in this broad, unselected population is itself a remarkable finding. It suggests that dysregulation of the bile acid signaling pathway may be a far more common and central feature of refractory CC than is currently appreciated. It is possible that many patients with clinically defined "normal transit" constipation actually have a subtle form of bile acid malabsorption or dysregulation that is corrected by IBAT inhibition. This highlights the most exciting future direction for this field. The ultimate goal is to move from the empirical success seen in these trials to true precision medicine.[16] This will require future studies that incorporate physiological testing at baseline. Imagine a trial where all patients undergo a colonic transit study and have their fecal bile acids measured. If, as hypothesized, the response to elobixibat is greatest in those with slow transit and low fecal bile acids, these tests could become clinical biomarkers to select patients most likely to benefit. This would allow clinicians to reserve the therapy for those with the highest chance of success, maximizing efficacy while minimizing unnecessary exposure to side effects for those with a different underlying pathophysiology, such as a primary defecatory disorder. Our meta-analysis, by confirming the potent but non-specific efficacy of elobixibat in a broad refractory population, provides the strongest possible rationale for conducting these future biomarker-driven studies.[17]



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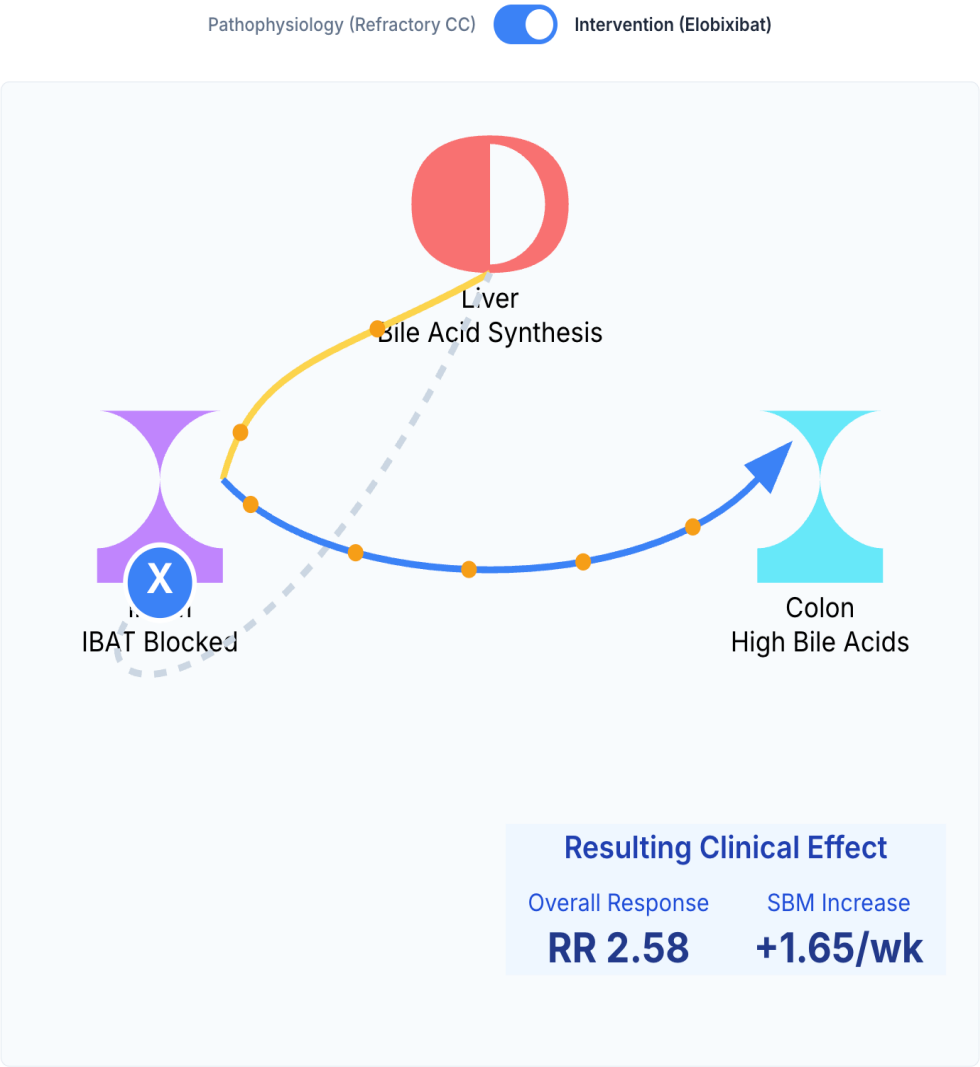

B

Figure 8. Pathophysiology mechanism and clinical correlates of IBAT inhibition. A. Pathophysiology (Refractory CC). B. Intervention (Elobixibat).

Figure 8 showed a detailed schematic diagram that elegantly contrasts the underlying pathophysiology of refractory chronic constipation with the therapeutic effect of the ileal bile acid transporter (IBAT) inhibitor, elobixibat, directly linking the pharmacological mechanism to the clinical outcomes quantified in the meta-analysis. Figure 8 is presented in two states. The first state illustrates the pathophysiology of refractory constipation. It depicts the liver synthesizing bile acids, which then travel to the small intestine. The diagram highlights a crucial step in the ileum, where the IBAT transporter is shown to be highly efficient, leading to the reabsorption of the vast majority of these bile acids back into the enterohepatic circulation for return to the liver. The visual consequence of this efficient reuptake is a significantly diminished flow of bile acids into the colon.[18] This results in a physiological state of low colonic bile acid concentration. The figure explains that this lack of bile acids, which serve as natural agents to stimulate colonic motility and fluid secretion, culminates in the clinical condition of constipation, characterized by a

low baseline frequency of approximately 1.2 spontaneous bowel movements per week. The second state of the figure 8 demonstrates the profound impact of the pharmacological intervention with elobixibat. Here, the diagram shows elobixibat actively blocking the IBAT transporter in the ileum, visually represented by an 'X' over the reabsorption pathway. This targeted inhibition disrupts the normal reabsorption process. As a result, the primary route for bile acids is no longer back to the liver, but forward into the colon. This intentional redirection dramatically increases the concentration of bile acids within the colonic lumen, creating a state of high colonic bile acids. Crucially, the figure 8 connects this altered physiological state to the potent clinical effects observed in the study. The increased presence of bile acids in the colon stimulates both motility and secretion, correcting the underlying functional deficits of constipation. This mechanistic action is directly correlated with the key efficacy findings from the meta-analysis, which are displayed in a results-oriented callout box.[19] The diagram shows that this intervention leads to an overall clinical response with a Risk Ratio of 2.58 compared to placebo, and a clinically significant mean increase of 1.65 spontaneous bowel movements per week. In essence, the figure provides a clear, narrative-driven visual model that seamlessly bridges the gap from the molecular mechanism of IBAT inhibition to the substantial and statistically significant clinical benefits for patients suffering from refractory chronic constipation.[20]

5. Conclusion

This study provides definitive, high-level evidence that the ileal bile acid transporter inhibitor elobixibat is a powerful and effective therapeutic agent for patients with chronic constipation who have failed conventional treatments. By targeting a core physiological pathway, elobixibat offers a substantial improvement in bowel function, with one additional patient achieving a clinically meaningful response for every five treated. This robust efficacy solidifies its role not merely as another option, but as a cornerstone therapy in the management of complex, refractory constipation. The potent pro-secretory and prokinetic effects of elobixibat, however, come with an inherent and predictable trade-off. The significant risk of gastrointestinal side effects, particularly diarrhea and abdominal pain, is a direct consequence of its intended mechanism. This duality underscores the central clinical challenge: leveraging the drug's power while mitigating its adverse effects. The successful use of elobixibat in clinical practice will therefore depend on careful patient selection, judicious dose titration, and a thorough, transparent dialogue with patients about this benefit-risk calculus. Ultimately, elobixibat redefines the therapeutic ladder by introducing a distinct and potent mechanistic target. Its availability compels a more sophisticated, pathophysiology-driven approach to refractory constipation, moving clinicians beyond a simple stepwise algorithm toward a more personalized selection of therapy. While the promise of precision medicine—identifying the ideal patient phenotype for IBAT inhibition—awaits future research, the evidence presented here firmly establishes elobixibat as a critical tool for alleviating the burden of one of the most challenging conditions in gastroenterology.

6. References

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