Evaluation of Therapeutic Risk/Benefit Ratios From Pooled Plecanatide and Linaclotide Phase 3 Trials in Adult Patients With Chronic Idiopathic Constipation (CIC)

Darren M. Brenner, MD[1]; Tim Mikhelashvili, PharmD[2]; Gregory Sayuk, MD, MPH[3]

[1]Divison of Gastroenterology, Northwestern University–Feinberg School of Medicine, Chicago, IL, USA; [2]Synergy Pharmaceuticals Inc., New York, NY, USA; [3]Division of Gastroenterology, Washington University, St Louis, MO, USA

Introduction

- The FDA has approved 3 secretagogues for the treatment of adults with chronic idiopathic constipation (CIC): plecanatide, linaclotide, and lubiprostone.
- Plecanatide and linaclotide are guanylate cyclase-C (GC-C) receptor agonists, whereas lubiprostone is a type 2 chloride channel activator.[1-3]
- Plecanatide is the structural analog of the naturally occurring human GI peptide uroguanylin and replicates its pH-sensitive activity in preclinical studies.[4] Preclinical studies have demonstrated that linaclotide activity is pH independent.[5]
- While clinical trials are the gold standard of efficacy and safety data, healthcare providers often look to other analyses of these data to evaluate benefit/risk in clinical practice.
- Calculating the number needed to treat (NNT) and the number needed to harm (NNH) may help determine whether a treatment will be helpful or harmful.[6]
  - NNT provides an indicator of therapeutic benefit (ie, efficacy relative to placebo), whereas NNH provides an indicator of therapeutic risk (ie, relative safety using the adverse event [AE] profile vs placebo).
  - The likelihood to be helpful or harmful (LHH) is calculated as the NNH:NNT ratio, with ratios >1 indicative of relative benefit and ratios <1 indicative of relative risk.
- Despite the potential limitations of NNT and NNH calculations, these values may facilitate clinician assessment of both benefits and risks of medications within a therapeutic class.

Objective

- To provide a clinical perspective on the therapeutic risks and benefits with FDA-approved doses of plecanatide and linaclotide, by calculating NNT, NNH, and LHH values using pooled data from phase 3 clinical trials in CIC.

Methods

- Due to significant differences in phase 3 trial designs (eg, duration, endpoints), lubiprostone was not included in these analyses.
- Data included for analysis were from five phase 3 clinical trials in adults with CIC, consisting of similar patient populations and identical treatment durations. The approved doses of plecanatide (3 mg) and linaclotide (72 mcg and 145 mcg) were evaluated (**Table 1**).[7-10]

Table 1. Characteristics of Included Studies of Approved Doses

	Study 1[7]	Study 2[8]	Study 3[9]	Study 4[9]	Study 5[10]	
Registration Identifier	NCT01982240	NCT02122471	NCT00765882	NCT00730015	NCT02291679	
Treatment	Plecanatide 3 mg vs placebo	Plecanatide 3 mg vs placebo	Linaclotide 145 mcg vs placebo	Linaclotide 145 mcg vs placebo	Linaclotide 145 mcg vs placebo	Linaclotide 72 mcg vs placebo
Design	12-week, phase 3, double-blind, placebo-controlled, randomized clinical trial		12-week, phase 3, double-blind, placebo-controlled, randomized clinical trial			
Diagnostic Tool	Modified Rome III criteria for CIC		Modified Rome II criteria for CIC		Modified Rome III criteria for CIC	
Patient Population*	% male: 18.8% Mean age: 45.0 % white: 66.7%	% male: 22.1% Mean age: 45.5 % white: 77.0%	% male: 8.5% Mean age: 49 % white: 78.9%	% male: 12.0% Mean age: 47 % white: 75.6%	% male: 23.6% Mean age: 46.8 % white: 71.5%	% male: 24.1% Mean age: 45.8 % white: 72.5%
Primary Efficacy Endpoint	Durable overall CSBM responder		Overall CSBM responder			
Efficacy Population*	453	467	213	217	411	411
Safety Population*	474	443	430†		411	411

CSBM, complete spontaneous bowel movement. *For corresponding treatment. †Safety data were presented as pooled data in the original report.[9]

Efficacy/NNT

- The primary efficacy endpoint in the linaclotide trials was the percentage of patients who were overall complete spontaneous bowel movement (CSBM) responders during the 12-week treatment period.
  - A CSBM weekly responder was defined as a patient who had ≥3 CSBMs for a given week and an increase from baseline of ≥1 CSBM/week for that same week. An overall CSBM responder was a patient who was a weekly CSBM responder for ≥9 of the 12 treatment weeks.
- The primary efficacy endpoint in the plecanatide trials was the percentage of patients who were **durable** overall CSBM responders during the 12-week treatment period, which included those who were an overall CSBM responder **plus a weekly responder in ≥3 of the last 4 weeks** of treatment, a more stringent endpoint.
- NNT addresses the question of how many patients a clinician would need to treat with a given medication before one would expect a positive outcome of interest.[6]
  - NNT=1/(net active treatment efficacy minus placebo)

Safety/NNH

- In the plecanatide and linaclotide studies, AEs were collected at clinical visits by unsolicited spontaneous report or in response to open-ended non-leading questions.
  - The plecanatide trials did not allow for any dose interruption due to an AE, with patients discontinuing treatment if they could not tolerate the medication and had an AE, including diarrhea.
  - Patients in the linaclotide trials were permitted to temporarily suspend dosing for up to 3 days in the event of an AE. Additional dose interruptions were permitted upon discussion with the medical monitor of the trial. Therefore, linaclotide-treated patients could stop the medication and see if the AE resolved before resuming dosing.
- NNH answers the question of how many patients a clinician would need to treat with a given medication before one would expect a negative outcome.[6]
  - NNH=1/(net diarrhea rate of active treatment minus placebo)
- In an additional analysis, the NNH for discontinuations due to AEs (NNH-D) was determined.
  - NNH-D=1/(net discontinuations due to AEs of active treatment minus placebo)

NNH/NNT Ratio

- LHH=NNH/NNT
  - Provides an indication of relative therapeutic risk/benefit or likelihood of a treatment to be helpful or harmful.
  - Ratio >1 is indicative of positive benefit-risk profiles.
- LHH-D (discontinuation due to an AE)=NNH-D/NNT
  - Ratio >1 is indicative of positive benefit-risk profiles.

Results

Table 2. Calculations for Derived Parameters

A. NNT

	Plecanatide 3 mg (2 RCTs; pooled data)		Linaclotide 72 mcg (1 RCT)		Linaclotide 145 mcg (3 RCTs; pooled data)	
Parameter	Active	Placebo	Active	Placebo	Active	Placebo
Efficacy Endpoint Responder Rate (%)	20.5%	11.5%	12.4%	4.7%	13.8%	4.5%
Net Efficacy Rate (active – placebo) (%)	9.0%		7.7%		9.3%	
NNT (1/Net Efficacy Rate)	11.1		13.0		10.8	

B. NNH and LHH

	Plecanatide 3 mg (2 RCTs; pooled data)		Linaclotide 72 mcg (1 RCT)		Linaclotide 145 mcg (3 RCTs; pooled data)	
Parameter	Active	Placebo	Active	Placebo	Active	Placebo
Diarrhea Rate (%)	4.6%	1.3%	19.2%	7.0%	19.0%	5.8%
Net Diarrhea Rate (active – placebo) (%)	3.3%		12.2%		13.2%	
NNH (1/Net Diarrhea Rate)	30.3		8.2		7.6	
LHH (NNH/NNT)	2.7		0.6		0.7	

C. NNH-D and LHH-D

	Plecanatide 3 mg (2 RCTs; pooled data)		Linaclotide 72 mcg (1 RCT)		Linaclotide 145 mcg (3 RCTs; pooled data)	
Parameter	Active	Placebo	Active	Placebo	Active	Placebo
Discontinuation Rate (%)	4.1%	2.2%	2.9%	0.5%	6.3%	2.4%
Net Discontinuation Rate (active – placebo) (%)	1.9%		2.4%		3.9%	
NNH-D (1/Net Discontinuation Rate)	52.6		41.7		25.6	
LHH-D (NNH-D/NNT)	4.7		3.2		2.4	

AE, adverse event; CSBM, complete spontaneous bowel movement; ITT, intent-to-treat; LHH, likelihood to be helped or harmed (diarrhea); LHH-D, likelihood to be helped or harmed–discontinuation due to AE; NNT, number needed to treat; NNH, number needed to harm (diarrhea); NNH-D, number needed to harm–discontinuation due to AE; RCT, randomized controlled trial.

Figure 1. (A) Number Needed to Treat and (B) Number Needed to Harm (Diarrhea)

- In the pooled phase 3 CIC trials, the NNT was 11.1 with plecanatide 3 mg, 13.0 with linaclotide 72 mcg, and 10.8 with linaclotide 145 mcg (**Table 2A**, **Figure 1A**).
- The NNH (using diarrhea as the outcome) was 30.3 with plecanatide 3 mg, 8.2 with linaclotide 72 mcg, and 7.6 with linaclotide 145 mcg (**Table 2B**, **Figure 1B**).

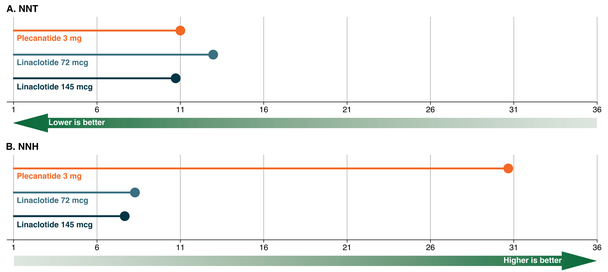


Figure 2. Number Needed to Harm (Discontinuations due to AEs)

- The NNH-D (using discontinuation due to AEs as the outcome) was 52.6 with plecanatide 3 mg, 41.7 with linaclotide 72 mcg, and 25.6 with linaclotide 145 mcg (**Table 2C**, **Figure 2**).

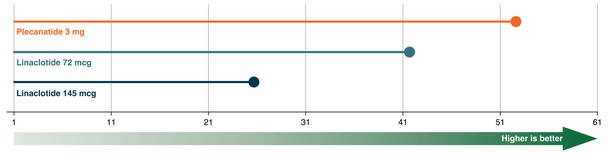


Figure 3. Likelihood of Treatment to Be Helpful or Harmful (Diarrhea)

- The LHH values for plecanatide 3 mg, linaclotide 72 mcg, and linaclotide 145 mcg were 2.7, 0.6, and 0.7, respectively, representing a 4.5-fold and 3.9-fold difference favoring plecanatide 3 mg over linaclotide 72 mcg and 145 mcg, respectively (**Table 2B**, **Figure 3**).

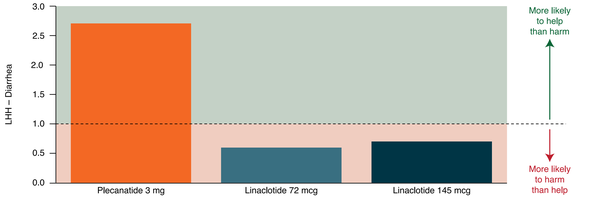
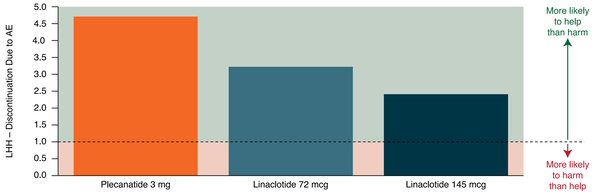


Figure 4. Likelihood of Treatment to Be Helpful or Harmful (Discontinuations due to AEs)

- The LHH-D for plecanatide was 4.7, while the LHH-D was 3.2 and 2.4 for linaclotide 72 mcg and 145 mcg, respectively, representing a 1.5-fold and 2-fold difference favoring plecanatide 3 mg over linaclotide 72 mcg and 145 mcg, respectively (**Table 2C**, **Figure 4**).



Discussion

- **Lower NNT values indicate that fewer patients need to be treated in order to see a clinical benefit, with plecanatide and linaclotide demonstrating similar values.**
- **Two analyses of NNH were conducted using 2 clinically relevant "harms"—treatment-emergent diarrhea and discontinuation due to an AE.**
  - **Higher NNH values indicate a larger number of patients need to be treated in order to see a detrimental effect.**
  - **The NNH value for plecanatide was approximately 3-fold higher than the NNT value, indicating that plecanatide patients are 3 times more likely to have a beneficial effect rather than a harmful effect.**
  - **The NNH values for linaclotide 72 mcg and 145 mcg were each lower than the respective NNT values, indicating that, for both doses of linaclotide, patients are more likely to experience a harmful effect before experiencing a beneficial effect.**
- **The comparatively high LHH values in the plecanatide CIC trials indicate a favorable benefit/risk profile.**
- **For both LHH and LHH-D analyses, the ratio with plecanatide was >1, indicating that treatment with plecanatide 3 mg is more likely to help than to harm a patient (2.7 times for diarrhea and 4.7 times for LHH-D).**
- **In the LHH analysis, neither linaclotide dose resulted in LHH >1 (0.6 and 0.7 for the 72 mcg and 145 mcg doses in the analysis of treatment-emergent diarrhea) and thus were more likely to harm than to help a patient. The LHH-D analysis showed both doses of linaclotide to have a positive risk/benefit profile.**
- **In the absence of head-to-head clinical trials, such analyses may represent an important facet in clinical decision-making when considering prescription options for the treatment of CIC.**

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