Asimadoline and its potential for the treatment of diarrhea-predominant irritable bowel syndrome: a review

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Abstract: Irritable bowel syndrome (IBS) is a multifactorial condition with principal symptoms of pain and altered bowel function. The kappa-opioid agonist asimadoline is being evaluated in Phase III as a potential treatment for IBS. Asimadoline, to date, has shown a good safety profile and the target Phase III population – diarrhea-predominant IBS patients with at least moderate pain – was iteratively determined in a prospective manner from a Phase II dose-ranging study. The clinical data in support of this population are reviewed in this article. Furthermore, the scientific rationale for the use of asimadoline in the treatment of IBS is reviewed. Considering the high patient and societal burdens of IBS, new treatments for IBS represent therapeutic advances.

Keywords: irritable bowel syndrome, kappa-opioid agonist, asimadoline, visceral pain, visceral hypersensitivity

Introduction

Irritable bowel syndrome (IBS) remains one of the most common disorders seen by gastroenterologists. 1-3 Although IBS itself does not lead to a more sinister pathology, the magnitude and importance of the symptoms associated with IBS result in patients undergoing more surgical procedures in search of other etiologies to explain and treat their symptoms, reduced quality of life, increased health care expenditures, increased work absenteeism, reduced productivity while at work, and increased psychological disorders. 3-11 Thus, the burden of IBS on the patient and in terms of societal costs is large. Considering this, finding new, safe, and efficacious treatments for IBS is of large importance both at the patient level and also to reduce the overall burden on the health care system.

IBS has been estimated to have a prevalence of approximately 6%-12% in Western countries. 9,12-14 Most studies show IBS to be a disorder predominantly in females, with a female-to-male ratio of 2-2.5 to 1. In many patients, symptoms begin in childhood or young adulthood, and often continue throughout their lives with an episodic course of exacerbations and remissions.

The principal symptoms of IBS are abdominal pain and altered bowel function. 15 The alterations in bowel function may manifest as diarrhea, constipation, or an alternation between the two bowel states. These abnormal bowel patterns have led to subtyping of IBS as diarrhea-predominant IBS (D-IBS), constipation-predominant IBS (C-IBS), and mixed or alternating IBS (A-IBS). 15 As discussed later in this review, the abdominal pain associated with IBS is a consequence of a state of heightened visceral nociception. 15
Effective treatments for IBS need to improve both abdominal pain and abnormal bowel patterns. To date, few contemporary agents have obtained regulatory approval for the treatment of IBS. In considering a reasonable profile for future IBS treatments, several features should be noted. First, there should not be the expectation that a single agent will be efficacious in more than one subtype of IBS. Present-day agents have been shown to be efficacious in only one IBS subtype, reflecting that improvement by the same agent for states of both diarrhea and constipation is unlikely. This presents challenges for the treatment of the A-IBS population. Some have proposed to study A-IBS patients in either their diarrheal or their constipated states, and then combine those populations with either D-IBS or C-IBS patients for indications of nonconstipated IBS patients or constipated IBS patients, respectively. We believe that to achieve these indications, it would be most appropriate to have completed long-term safety information both in D-IBS or C-IBS patients and in an all-comer population of A-IBS patients. A-IBS patients in their diarrheal phase will eventually alternate from their state of diarrhea to constipation; therefore, an all-comer A-IBS population should be used in safety studies. Second, effective IBS treatments must treat abdominal pain. Agents that treat only abnormal bowel function in IBS patients may be classified as laxatives or antidiarrheals, but are not IBS treatments just because they treat abnormal bowel function in IBS patients. Third, in evaluating datasets from randomized, placebo-controlled IBS studies, relevant subgroups should be considered. For all datasets in IBS patients, analyses should be conducted on patients stratified by gender and IBS subtype. Depending on the specific agent, other prespecified analyses may include efficacy by baseline pain. Finally, duration of action ideally should persist as long as treatment does. Some agents show a dissipation of effect with continued treatment. However, this latter point has not been and is not an absolute barrier to drug approval.

When evaluating currently available therapeutic options for the treatment of IBS, few drugs have regulatory approval. For D-IBS patients, alosetron remains the gold standard therapy with respect to drug efficacy. Alosetron shows excellent efficacy in the treatment of multiple symptoms of IBS in diarrhea-predominant patients. Most notably, improvement is seen on adequate relief of IBS pain and discomfort, urgency, stool consistency, and stool frequency. However, the potential use of alosetron will always be limited by its safety profile. With alosetron, significant constipation occurred in approximately 25% of the patients enrolled in clinical trials. Constipation was responsible for the withdrawal of approximately 10% of patients from clinical trials, and ischemic colitis was also reported in association with the use of alosetron.

The only other agent for which regulatory approval for D-IBS has been sought in contemporary time is rifaximin. Rifaximin shows marginal efficacy, with differences of rifaximin over placebo in the two pivotal studies of approximately 9% on the primary endpoint. Evaluation of abdominal pain also showed benefit of less than a 10% difference with rifaximin as compared with placebo. For several endpoints, efficacy with rifaximin dissipated over time in the 10-week observation period following 2 weeks of dosing. The initial new drug application (NDA) for rifaximin in the treatment of IBS was rejected due to lack of long-term safety or repeat-use data.

At the time of the writing of this manuscript, the kappa-opioid agonist asimadoline is in Phase III development for the treatment of D-IBS patients. The available data on asimadoline as a potential treatment for IBS are reviewed in this manuscript.

For the treatment of C-IBS, tegaserod showed benefit on multiple symptoms in C-IBS patients, but tegaserod was ultimately withdrawn from marketing because of cardiovascular safety concerns. Lubiprostone is indicated for the treatment of patients with C-IBS. Efficacy with lubiprostone is not robust, with differences on the primary endpoint as compared with placebo of 7.8% (17.9% vs 10.1%). Evaluation of data during the individual months of treatment showed significance in one Phase III study only at month 2, and in the other study at months 2 and 3. Magnitudes of improvement in pain were not clinically relevant.

Based on the publicly available data, we believe that linaclotide for the treatment of C-IBS will achieve regulatory approval. Linaclotide shows statistically significant benefit on multiple endpoints including bowel movement frequency, pain, straining, bloating, and stool consistency.

**Asimadoline: a peripherally restricted kappa-opioid receptor agonist**

For a putative opioid agonist or antagonist, the importance of selectivity across opioid class receptors should not be underestimated. The effects and side effects of centrally active analgesic mu-opioid receptor agonists, such as euphoria, respiratory depression, tolerance, dependence, and withdrawal, can be significant, especially if agents are used as chronic treatments. Peripherally restricted mu-opioid receptor agonists (eg, loperamide) are powerful antidiarrheal...
agonists have been shown to block sodium channels at high concentrations. Although arylacetamide kappa-opioid receptors have no affinity below the micromolar range for any other receptor subtype, asimadoline is also highly specific, demonstrating a half-maximum inhibitory concentration (IC_{50}) of 1.2 nM (Ki, 0.6 nM) was determined in radioligand binding assays using human recombinant kappa-opioid receptors expressed in CHO cells. Studies in preclinical species revealed a similar high affinity binding of asimadoline at guinea pig brain kappa receptors (IC_{50}, 3–6 nM). Asimadoline is a potent, full agonist at kappa-opioid receptors in functional assays using rabbit vas deferens and guinea pig ileum.

Asimadoline is highly selective for kappa-opioid receptors, having approximately 400- to 500-fold lower affinity for recombinant human mu-opioid (IC_{50}, 601 nM; Ki, 216 nM) or delta-opioid (IC_{50}, 597 nM; Ki, 313 nM) receptors expressed in CHO cells. Studies in preclinical species revealed a similar high-affinity binding of asimadoline to guinea pig brain kappa receptors (IC_{50}, 3–6 nM). Asimadoline is a potent, full agonist at kappa-opioid receptors in functional assays using rabbit vas deferens and guinea pig ileum.

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observed with concomitant administration of ketoconazole. However, even in the presence of this enhanced exposure, equivalent to eight times the $C_{\text{max}}$ reached during 0.5 mg bid dosing (the target IBS dose), there were no effects upon any of the measured CNS endpoints. It was concluded that the threshold for CNS effects of asimadoline is at least ten-fold higher than drug levels achieved in the IBS setting, in good agreement with the experience from clinical safety and efficacy studies performed to date.

**Visceral analgesic and antihyperalgesic actions**

Kappa-opioid receptors are members of the superfamily of inhibitory GTP-binding regulatory protein (G protein)-coupled receptors, which activate potassium channels, inhibit calcium channels, and inhibit adenylate cyclase activity, all resulting in an inhibition of neuronal excitability.46 Kappa-opioid receptors are thought to be located on the terminals of a variety of neurons, including those extrinsic visceral afferent neurons that transmit sensory signals from the gut to the CNS.40–45 A broad literature46 describes a peripherally mediated, visceral analgesic and antihyperalgesic activity of kappa-opioid receptor agonists.

The fundamental mechanism of action for production of the visceral analgesic effect of kappa-opioid receptor agonists is an inhibition of the excitability of visceral afferent nerve terminals in the gut wall, causing a reduction of action potential firing and neurotransmitter release from those sensory nerves.46 An action in the CNS does not appear to be necessary for visceral analgesia with kappa-opioid receptor agonists.41–43 However, the presence of visceral hypersensitivity is thought to be important for optimum visceral analgesic effect of kappa-opioid receptor agonists.45,47,48 The analgesic potency of asimadoline is increased in visceral pain models in the presence of visceral hypersensitivity.47,48 Previous studies in somatic pain models demonstrated that the potency of asimadoline’s analgesic effect is higher following the induction of hyperalgesia.26 Such antihyperalgesic effects may be produced by asimadoline’s abilities to reduce expression of substance P and calcitonin gene-related peptide in dorsal root ganglia (DRG) neurons in chronic hyperalgesia and to inhibit plasma extravasation and the release of neurogenic inflammatory mediators.26,49,50

Recently, data from studies of peripheral sensory nerves (trigeminal ganglion) in rats suggest that peripheral kappa-opioid receptors require stimuli associated with sensitization processes to become functional.51 Such induction of “functional competence” of kappa-opioid receptors by sensitizing agents (e.g., bradykinin) involves the phospholipase C pathway, arachidonic acid metabolism, and membrane integrins. Earlier work described kappa-opioid receptors in peripheral sensory nerves as dormant “silent” receptors, showing that neuronal depolarization stimulates kappa-opioid receptor mRNA expression, axonal transport, and protein translation in DRG neurons.52–55 The authors described a membrane depolarization-induced de novo synthesis of kappa-opioid receptors in DRG that was mediated by a netrin-1-induced translocation of mRNA to the transcriptionally active polyribosomal fraction. The effect was dependent on calcium influx via L-type calcium channels, and Copb1-dependent trafficking of mRNA along axons was also demonstrated. Such neuronal activity-dependent and/or sensitization-dependent increases in kappa-opioid receptor expression and function may underlie the preferential efficacy of asimadoline in hypersensitive states both in animal models and in man.

Pharmacodynamic studies with asimadoline also suggest a preferential efficacy against visceral pain in patients with visceral hypersensitivity. Delvaux et al45 evaluated asimadoline for potential analgesic activity in IBS patients with significant pain symptoms and demonstrated visceral hypersensitivity (pain threshold $\leq$32 mmHg). The crossover study design compared the effect of single doses of placebo with 0.5 mg asimadoline upon distensions over a range of pressures up to 45 mmHg. Asimadoline produced a significant reduction of the AUC of pain intensity (rated at each distension step) and a small but nonsignificant increase in pain threshold, compared with placebo. No effect on colonic compliance or perception of nonpainful distensions was observed. Delgado-Aros et al56 performed similar barostat studies in healthy volunteers. The parallel-group study compared single doses of placebo with 0.15 mg, 0.5 mg, and 1.5 mg asimadoline. Colonic distensions at 8 mmHg, 16 mmHg, 24 mmHg, and 32 mmHg were rated for gas and pain perception scores using a 100 mm visual analogue scale (VAS). Although pain scores were lower in the 0.5 mg dose group at all distension levels, the differences were not statistically significant, including at the two higher pressure distension levels, which elicited pain scores of 40–50 mm on the VAS, suggesting that kappa receptor activation does not significantly inhibit moderate to high-level noxious sensations in health. Asimadoline at 0.5 mg and 1.5 mg had mixed inhibitory or excitatory effects on low-threshold gas and pain sensations in response to low pressure (8 mmHg and 16 mmHg) distension, which were scored below 35 mm on the VAS. This
suggests a potential role for kappa receptors in modulation of less noxious sensations in the “nonsensitized” state of health. The findings from these two studies correlate with the clinical experience gained to date from efficacy and safety studies with asimadoline, in which efficacy against symptoms of IBS is greatest in patients with a higher symptom burden.57

**Antidiarrheal actions**

Kappa receptors are found on cholinergic terminals of enteric neurons of the myenteric plexus where they inhibit cholinergic transmission and inhibit propulsive motility when studied in vitro.58,59 However, there is a paucity of data concerning any role of kappa-opioid receptors in gastrointestinal secretion. Immunohistochemistry studies in gastrointestinal tissues from pig,60 rat,61 and guinea pig62 demonstrate a preferential distribution of kappa-opioid receptors in the myenteric plexus, with either low or no immunoreactivity found in submucous plexus neurons where mu-opioid receptors predominate. However, in mice the opposite distribution has been described for kappa-opioid receptors, along with an up-regulation of these receptors in the submucous plexus during inflammation.61 Asimadoline has no effect on normal gastrointestinal transit in the small intestine in mice26 or on colonic transit or postprandial motility in healthy normal gastrointestinal transit in the small intestine in mice26 or on guinea pig62 demonstrate a preferential distribution of kappa-opioid receptors in the myenteric plexus, where they inhibit Kappa receptors are found on cholinergic terminals of cholinergic transmission and inhibit propulsive motility when studied in vitro.58,59 However, there is a paucity of data concerning any role of kappa-opioid receptors in gastrointestinal secretion. Immunohistochemistry studies in gastrointestinal tissues from pig,60 rat,61 and guinea pig62 demonstrate a preferential distribution of kappa-opioid receptors in the myenteric plexus, with either low or no immunoreactivity found in submucous plexus neurons where mu-opioid receptors predominate. However, in mice the opposite distribution has been described for kappa-opioid receptors, along with an up-regulation of these receptors in the submucous plexus during inflammation.61 Asimadoline has no effect on normal gastrointestinal transit in the small intestine in mice26 or on colonic transit or postprandial motility in healthy normal volunteers,66 but inhibits stress-induced fecal output in rats (Tioga Pharmaceuticals, Inc, unpublished data) and reduces diarrhea in D-IBS patients without producing constipation.57 Thus, although kappa-opioid receptors are found in the ENS, they do not appear to be critical mediators of normal motility and secretory processes in the normal state. The lack of a constipating effect of kappa receptor agonists in D-IBS may be due to their preferential localization in the myenteric plexus such that secretory processes are not inhibited; in addition, their presynaptic localization may allow for a more subtle modulation of motility in contrast to the stronger inhibitory influence on both motility and secretion produced by the broader localization of mu-opioid receptors both presynaptically and on cell bodies of both myenteric and submucosal plexus neurons.60–62 In addition, a similar reliance upon a hypersensitizing stimulus for receptor functionality, as described above for peripheral sensory nerves, may exist in the ENS, especially in the submucous plexus.63

It is also possible that the effect of asimadoline on sensitized gastrointestinal transit may also be mediated by a non-ENS site of action. Several studies have demonstrated altered postprandial motility and symptoms in functional bowel disorder patients. Of note in D-IBS patients are increased small bowel motility,64 faster oroceleonic transit,65 faster ileocolonic transit,66 increased colonic motility index, greater number of high amplitude propagating contractions and shortened colonic transit time,67 and increase in meal-related or postprandial symptoms.68 Such enhanced “gastrocolic” responses may be the result of hypersensitivity in the extrinsic vagal and or spinal nerves that mediate these reflexes, and inhibition of these enhanced reflexes is an interesting potential mechanism of action for asimadoline in the reduction of diarrhea and other symptoms in these patients.

**Clinical trials with asimadoline in the treatment of IBS**

Based on the results of the barostat study in IBS patients,45 a randomized, multicenter, placebo-controlled, dose-ranging IBS trial was conducted with asimadoline.59,69 This Phase IIb trial enrolled approximately 600 patients, including patients with all three IBS subtypes, as well as male and female IBS patients. Prospectively defined subgroup analyses were done by degree of baseline pain, as well as by gender and IBS subtype.

In the intent-to-treat population, asimadoline at doses of 0.15 mg, 0.5 mg, or 1.0 mg was given bid and no dose level distinguished itself from placebo (bid). Following the prospectively planned analysis scheme, numerically and statistically significant benefit was seen with all doses of asimadoline in patients with higher levels of baseline pain.57,69 One-third of the patients who entered the trial with the highest level of baseline pain showed excellent benefit on multiple endpoints. Similar benefit was seen in both genders, but efficacy was driven by D-IBS patients. Thus, the Phase IIb study identified a target population for progression into Phase III of male and female D-IBS patients who had more severe pain at baseline. For ease of recruitment into the Phase III program, the target population became D-IBS patients with at least moderate pain at baseline. Analyses of this population from the Phase IIb data yielded excellent efficacy results on pain scores (Figure 1), stool frequency (Figure 2), pain-free days, urgency, bloating, and adequate relief.57

By contrast to the above study, a single-center study that analyzed data on the basis of on-demand or as-needed use did not show efficacy of asimadoline.70 The reason for the lack of efficacy is unclear.

Asimadoline has an extensive safety database.69,71 More than 1000 humans have been exposed to asimadoline in clinical trials. Single doses of asimadoline as high as 15 mg and repeat doses up to 10 mg administered daily for up to 8 weeks.
Figure 1 Effects of asimadoline on pain scores in D-IBS patients with at least moderate pain at baseline: asimadoline (asi) and placebo were administered twice daily for up to 12 weeks. Pain scores were collected daily and averaged numerically on a weekly basis. Week 0 represents the 2-week baseline period. As is apparent, with 0.5 mg and 1.0 mg dose levels, a substantial reduction in pain occurred, compared with placebo. Copyright © 2008. Reproduced with permission from Alimentary Pharmacology & Therapeutics.


Note: a P, 0.05; b P, 0.10.

Abbreviation: D-IBS, diarrhea-predominant irritable bowel syndrome.

Figure 2 Effects of asimadoline (asi) on stool frequency in D-IBS patients with at least moderate pain at baseline: asimadoline (0.5 mg) and placebo were administered twice daily for up to 12 weeks. Stool frequency was collected daily and averaged numerically on a weekly basis. Week 0 represents the 2-week baseline period. As is apparent, with the 0.5 mg dose level a substantial reduction in stool frequency occurred, compared with placebo.

Notes: Bars represent standard errors. Data provided by Tioga Pharmaceuticals, San Diego, CA. a P < 0.05; b P < 0.10.

Abbreviation: D-IBS, diarrhea-predominant irritable bowel syndrome.
Table 1 | Most common adverse events seen in nonirritable bowel syndrome asimadoline trials

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Percentage of patients with adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 224)</td>
</tr>
<tr>
<td></td>
<td>Asimadoline dose, twice daily</td>
</tr>
<tr>
<td>Headache</td>
<td>8%</td>
</tr>
<tr>
<td>Thirst</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4%</td>
</tr>
<tr>
<td>Polyuria</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
</tr>
<tr>
<td>Constipation*</td>
<td>0%</td>
</tr>
</tbody>
</table>

Note: Although no cases of constipation were reported, this is listed due to the importance of constipation in a D-IBS population. Data provided by Tioga Pharmaceuticals, San Diego, CA.

Abbreviation: D-IBS, diarrhea-predominant irritable bowel syndrome.

Table 2 | Most common adverse events in Phase IIb irritable bowel syndrome asimadoline trial among D-IBS patients with at least moderate pain at baseline

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Number of patients with adverse event (Asimadoline dose, twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 30)</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Data provided by Tioga Pharmaceuticals, San Diego, CA.

Abbreviation: D-IBS, diarrhea-predominant irritable bowel syndrome.

Figure 3 | Proposed mechanism of action of asimadoline in the treatment of D-IBS. (A) The “brain–gut” axis in the normal state (health). Sensory information is conveyed to the brain via the spinal cord (cylinder) by extrinsic VAN. Local reflexes and descending regulatory input from the CNS via autonomic efferent nerves (not shown) control overall gut function. Normal secretomotor function is coordinated by the ENS. (B) Visceral hypersensitivity in D-IBS drives increased activity in VAN resulting in increased sensory signaling to the brain and enhanced local reflexes, contributing to diarrhea. The accompanying transmitter release into the gut wall results in increased ENS activity (leading to diarrhea) and immune cell activation, which heightens sensitization. Kappa receptor expression on VAN terminals is up-regulated due to sensitization. (C) Asimadoline activates kappa-opioid receptors on VAN, leading to reduced sensory input to the brain, reduced local reflexes, and reduced transmitter release. Asimadoline also acts presynaptically to reduce neurotransmitter release in the ENS. Pain, diarrhea, and visceral hypersensitivity are reduced.

Abbreviations: CNS, central nervous system; D-IBS, diarrhea-predominant irritable bowel syndrome; ENS, enteric nervous system; VAN, visceral afferent nerves.
have been evaluated in various Phase I and Phase II studies. With the dosage level being evaluated in the Phase III asimadoline program, 0.5 mg bid, a very good safety profile has been observed (Table 1). Significantly, for a drug intended to treat D-IBS patients, no increase in constipation was reported. The most common adverse events seen in the Phase IIb IBS trial are shown in Table 2 for the efficacy population being evaluated in Phase III. Constipation is once again included, as it is a significant adverse event to consider in D-IBS patients. No safety signals were observed.

Conclusion
Treatment of patients with IBS remains a perplexing problem. Several confounding factors contribute to the difficulties in developing therapeutics. IBS is a multifactorial condition with principal symptoms of pain and altered bowel function. Pain is always a difficult symptom to treat. Furthermore, IBS is subtype into three principal groups, and the likely scenario is that the same medication will not work for more than one subtype of patients because of the difference in the type of bowel dysfunction. Additionally, although there are pharmacodynamic models by which to study transit and pain, there is no true animal model of IBS against which candidate therapeutics can be tested.

The kappa-opioid agonist asimadoline represents a potential treatment for IBS. Asimadoline, to date, has a good safety profile, and the target population showing strong efficacy was iteratively dissected from the Phase IIb data to optimize the likelihood of success in Phase III. There is a sound scientific basis for use of asimadoline in the treatment of IBS. Although an action of asimadoline in the ENS cannot be excluded, one potential mechanism of action that may explain all of the effects of asimadoline (on sensory and bowel function symptoms) in IBS is the activation of up-regulated kappa-opioid receptors on hypersensitive extrinsic afferent nerve terminals in the gut wall (Figure 3). This may result in (1) reduced sensory output from the gut to the spinal cord and brain, thereby directly inhibiting sensory symptoms and reducing augmented local motility reflexes that may contribute to sensory symptoms and diarrhea, and (2) reduced neurotransmitter release in the gut wall, which may lead to reduced diarrhea and potentially to a reduced level of peripheral, and subsequently central, sensitization in the brain–gut axis.

Disclosure
During the past year, A Mangel has participated in projects for the following sponsors: C-Path Institute, Tucson, AZ; Tioga Pharmaceuticals, San Diego, CA; Theravance, South San Francisco, CA; Novartis International AG, Basel, Switzerland; GlaxoSmithKline (GSK), London, UK; Pfizer, NY; and Boehringer, Binger Str, Ingelheim, Germany. A Mangel is an employee of RTI Health Solutions, Research Triangle Park, NC. RTI Health Solutions met the costs for preparation of this manuscript. G Hicks is an employee of Tioga Pharmaceuticals.

References


