BANNY WONG: Hi my name is Banny Wong. I'm a clinical fellow in the Division of Gastroenterology and Hepatology here at the Mayo Clinic in Rochester. Today, I'm talking about a novel first-in-class medication, called A3309. It's in the class of medicine called ileal bile acid transporter blocker. And we studied it for the treatment of functional constipation.

Chronic constipation has been a major problem and is a very common source of morbidity. And it raises health care costs, as well as diminishes quality of life. Patient dissatisfaction with standard laxatives are quite high, in spite of their widespread use. So there's really an unmet clinical need that exists for more effective, as well as safe, therapy for treating chronic constipation.

Now, we've previously studied bile acids and its effects on colonic function. And we found that giving primary bile acid, delivering it to the ileum in the colon, helps speed up transit and helps with the symptoms of constipation, as well.

So this medication, A3309, blocks the transporter that helps human beings reabsorb bile acid from the ileum. And when you block that, more bile acid leaks out into the colon. And that is postulated to help speed up transit by promoting colonic secretion, as well as motility, and to help with constipation symptoms, as well.

So our study involves a total of 36 patients. Our aim was basically to assess its effect on the transit of the GI tract, specifically the colon, as well as on symptoms of constipation.

We also evaluated some biochemical markers, where there's one called C4, which gives an idea as to how much bile acid the body is synthesizing. If you make the body lose bile acid by blocking its absorption, then you'll produce more bile acid to make up for that. So therefore, we anticipated that C4 will go up with the administration of A3309.

The 36 patients were all female. They all had functional constipation by Rome II criteria. And they were all adults at least 18 years of age up until 65 years of age. And their body mass index were all between 18 and 38.

None of them had any other GI disorders. And none of them were taking any medications that would affect transit of the gastrointestinal tract. They also all had baseline transit that's below the median of the normal population. So we want them to have relatively slow transit but not very slow.

This was a single-center study. It was randomized and then three parallel groups. It was also double-blinded, placebo-controlled, and is a Phase IIB pharmacodynamic study. The subjects all received 14 consecutive days of either placebo, or 15 milligrams of A3309, or 20 milligrams of A3309. So there were two doses used. And they all underwent colonic transit study by scintigraphy on the last three days of the study drug administration.

A primary endpoint was colonic transit at 24 hours. We also studied a variety of other transit endpoints, including gastric emptying, as well as small bowel transit. We also studied patients' symptoms in terms of their frequency of bowel movement, stool form, as well as their self-reported effectiveness of the drug, self-reported constipation rating. And then the biochemical markers involve C4, as we had talked about, as well as serum cholesterols.

On a primary endpoint, we found a statistically significant result. And the transit at 24 hours of the patient receiving A3309 for both doses were significantly faster. And it was also true at 48 hours. And the effect was very strong, in that the magnitude of effect was previously shown to be very significant at helping with symptoms of constipation, meaning increasing frequency of bowel movement, as well as softening the stool form.

And we actually confirmed that in this study, as well, when we found statistically significant effects on stool form, in terms of looser stools, and a trend towards increasing stool frequency with A3309. The patient also reported better ease of stool passage. And this effect was significant, as well.

Taking a look at treatment effectiveness, the patients also reported that the higher dose, the 20 milligram of A3309, was very effective at treating their constipation symptoms. They also reported a lower straining score, so they don't have to strain as much for a bowel movement.

In terms of the biochemical markers, we found a reversible increase in C4 with administration of both doses of the medicine. And there was about a three-fold increase in C4, consistent with the body having to make more bile acid in the liver to make up for the losses that this inhibitor of bile acid absorption is promoting.

And so this bile acid leaks into the colon and helps promote bowel movements and helps stool passage. And then it's lost in the stool, so the body will make more bile acid in the liver. And this is really consistent with that. After the medicine is stopped, the C4 level went back down to normal. So it's completely reversible.

The main side effects of the medication is mostly abdominal cramps and pain. And it was significantly higher with both dosages, with the higher dose causing a higher incidence of abdominal cramps and pain. But we found that the cramps and the pain of the abdomen was reported typically in association with having a bowel movement and that it would go away after a bowel movement.

So it tends to be associated with actually a desirable effect of the drug, which is to promote bowel movement to help with constipation. There's no other adverse events found in terms of serum laboratory tests, biochemistries, liver enzymes, as well as on EKGs.

So in summary, in functional constipation, we found that A3309 significantly sped up colonic transit. And it also induced beneficial effects on stool form, ease of passage, and on straining. A3309 also lead to a reversible increase in serum C4 levels, which is a marker of bile acid synthesis in the liver. This is consistent with our proposed mechanism that it blocks reabsorption of bile acid in the ileum. It is safe and well tolerated over the 14-day period.

Therefore, A3309 is really a modulator of enterohepatic circulation and is a novel first-in-class medicine that has potential in treating functional constipation. We believe that studies using longer-term administration, as well as repeated administration, of A3309 are warranted in order to more thoroughly study this drug's role in treating functional constipation and chronic constipation.

Thank you.