

AST-120 (spherical carbon adsorbent) Improves Pain and Bloating in a Randomized, Double-Blind, Placebo-Controlled Trial in Patients with Non-Constipating Irritable Bowel Syndrome (IBS)

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1. BACKGROUND

- Diarrhea-predominant IBS is a highly prevalent disorder, for which limited therapeutic options are available
- A safe and effective treatment for d-IBS patients is currently a large, unmet medical need
- The exact pathophysiology of d-IBS is unknown, and several intraluminal mediators have been implicated as potentially contributing to symptoms
 - These include:
 - Serotonin
 - Histamine
 - Lipopolysaccharide
 - Bile salts
 - Other mast cell degranulation products
- AST-120 is an oral, carbon-based adsorbent with extensive porosity and adsorbing capability
- It avidly adsorbs the mediators listed above from the lumen of the GI tract
- These actions, coupled with the known safety and tolerability profile of AST-120 in >360,000 Japanese patients, suggest that it should be a good candidate for the treatment non-constipating-IBS

2. METHODS

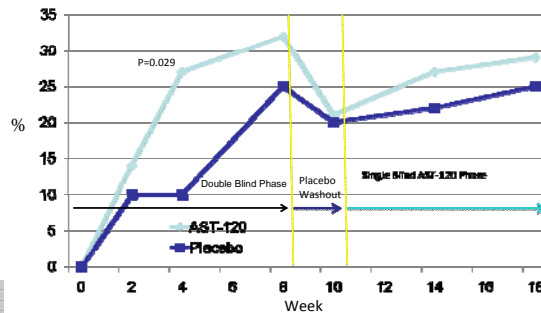
- Randomized, double-blind, placebo controlled trial was conducted in 115 patients with d/a-IBS
- After a 2-week run-in, patients received AST-120 2g po tid or a matching placebo over an 8-week randomized, double-blind treatment phase, followed by a 2-week placebo washout and an 8-week single-blind AST-120 phase
- The primary endpoint was the proportion of responders, defined as patients with $\geq 50\%$ reduction in days with pain over the previous 2-weeks as compared to baseline
- Pain severity and bloating severity were assessed on 100mm visual analogue scales

3. RESULTS

Demographics

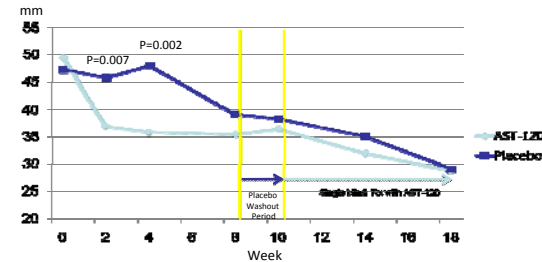
	AST-120	Placebo	Total
N	56	59	115
Age (mean)	47.3	45.7	46.5
Female (%)	64.3	62.7	63.5
Caucasian	89.3	84.7	87.0
USA (%)	57.1	59.3	58.3
d-IBS*	76.8	86.4	81.7

Primary Endpoint: Percent Responders * at Each 2 Week Interval



*Response defined as 50% reduction in days with pain

Bloating



*Bloating severity using 100 mm VAS

Treatment Emergent Adverse Events (Randomized Phase)

	AST-120	Placebo
Number of AEs	55	70
Number of Subjects with an AE	29 (51.8%)	33 (55.9%)
Most Frequent AEs in AST-120 Group (>5% and >placebo)		
Headache	6 (10.7%)	5 (8.5%)
Nausea	4 (7.1%)	4 (6.8%)
Constipation	3 (5.4%)	1 (1.7%)
Flu-Like Symptoms	3 (5.4%)	1 (1.7%)
Abdominal Pain	3 (5.4%)	0 (0.0%)
Abdominal Pain Upper	3 (5.4%)	0 (0.0%)
Vomiting	3 (5.4%)	0 (0.0%)

- $\geq 85\%$ of patients in each group completed the randomized phase. Almost 90% of patients complied with the oral sachet-dosing regimen
- At Week 8, the primary analysis time point, 32% of AST-120 subjects responded vs. 25% of placebo subjects. This difference was not statistically significant
- At Week 4, 27% of AST-120 patients responded compared to 10% of placebo patients, $p=0.029^*$.
- Response rates were similar regardless of gender or IBS subtype
- Pain severity was reduced by a mean of 11mm at Week 4 with AST-120 vs. 6mm for placebo
- Bloating severity was significantly reduced at Week 2 and Week 4 (see figure)
- AST-120 treatment reduced the impact IBS symptoms had on daily life compared to placebo.

*unadjusted, post hoc

- Over the entire 8-week randomized phase 21% of AST-120 patients achieved a 50% reduction in days with pain vs. 11% of placebo patients
- Benefit across multiple endpoints abated when AST-120 was discontinued and resumed once AST-120 was restarted
- Incidence of adverse events was 52% for AST-120 and 56% for placebo

4. CONCLUSIONS

- Based on the established safety profile and mechanism of action there is a strong rationale for studying AST-120 in the treatment of IBS patients
- This small, 115 patient, proof of concept study showed an increased response rate to AST-120 over placebo over an 8 week treatment course
- The strongest signal was seen after 4 weeks of therapy, at which time AST-120 demonstrated benefit across multiple endpoints
- Withdrawal of AST-120 was associated with loss of efficacy which returned with resumed treatment which adds additional support for efficacy signal
- No safety signals were identified that would preclude further evaluation as a treatment for IBS
- Larger studies of AST-120 in non-constipating IBS patients are warranted