IMPACT OF NGM282 ON THE INCIDENCE AND SEVERITY OF PRURITUS IN PRIMARY BILIARY CIRRHOSIS PATIENTS AND CORRELATIONS WITH LIVER CHEMISTRIES AND SERUM BILE ACIDS

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BACKGROUND

- Pruritus is a frequent comorbidity of patients with primary biliary cirrhosis (PBC) and other cholestatic liver diseases.
- The data supporting the pruritogenic role of elevated liver chemistries and serum bile acids (BAs) on the incidence and severity of pruritus are often conflicting and appear disease specific.
- Current treatment strategies include ursodeoxycholic acid, BA resins, rifampicin, sertraline and naltrexone but are variably effective.
- Recent investigational agents targeting ASBT enzyme inhibition have shown some correlation with decreases in serum BAs and pruritus.
- Other investigational agents (obeticholic acid) have been shown to be pruritogenic in patients with PBC.
- However, there is no data to date specifically correlating pruritus with either liver chemistries or serum BAs with treatments that specifically and potently suppress hepatic BA synthesis.
- NGM282 is a novel engineered variant of the enteric hormone FGF-19 which specifically inhibits CYP7A1, a key enzyme in the classic pathway of BA synthesis.
- Recent Phase 2 data with NGM282 in PBC patients demonstrated potent biologic activity with significant and rapid decrease in both serum liver chemistries and serum BAs.
- We investigated the impact of 28 days of NGM282 on the incidence and severity of pruritus at Baseline and change from Baseline in this same PBC population in order to:

1. Assess the risk for drug-induced pruritus
2. Evaluate and compare the clinical utility of the Visual Analogue Scale and the 5-D Itch Scale and measures for pruritus
3. Correlate the levels of serum liver chemistries and serum BAs on the incidence and severity with each measurement tool

METHODS

- Forty five subjects with an incomplete response to UDCA were randomized in a double blind fashion to NGM282 0.3 or 3 mg vs placebo as a daily SC injection for 28 days.
- There were no protocol exclusions for the presence, severity or treatment of pruritus at Baseline.
- Patients were evaluated for the incidence, severity and change in pruritus from Baseline using 2 standardized measurement tools:
  - ***Visual Analogue Score (VAS)***: Mono-dimensional scale where subjects mark on a 100 mm line a subjective assessment of their pruritus intensity: 0 = No pruritus and 100 = Unbearable pruritus [1]
  - ***5D Itch Scale***: Multi-dimensional questionnaire measuring five specific dimensions of pruritus: Duration (during the prior two weeks), Degree (intensity), Direction, Disability (sleep, work, standard activities) and Distribution on body [2]
- Patients were stratified by the presence of pruritus at Baseline using the 5D Itch Scale Question 2 assessing the presence and severity of pruritus during the 2 weeks prior to Baseline
- Pruritus was prospectively measured by Visual Analogue Scale (VAS) and the 5D Itch Scale at Baseline and Days 14, 28 and 42.
- Subjects with a Baseline and Day 28 assessment by VAS and/or 5D Itch Scale were categorized as improved, no change or worsened based on a >20% change from Baseline at Day 28 (VAS ≥ 20mm, 5D Itch ≥ 1 point).
- Correlations between pruritus and liver chemistries or serum BAs by VAS were assessed by Spearman correlation and regression analyses with a clinical anchor threshold of r=>0.30 and p=<0.05 as significant.
- Similar correlations between pruritus and liver chemistries or serum BAs for 5D Itch used an ANOVA without adjustment using the same thresholds for significance

RESULTS

- The study population was well-balanced across the 3 study arms and consistent with a typical PBC population (Table 1).
- Baseline pruritus was seen in 66.7%, 64.3% and 53.8% of the placebo, 0.3mg and 3 mg arms, respectively.
- The majority of patients with pruritus at Baseline had mild or moderate severity of pruritus, as measure by the 5D Itch.

Table 1. Study Population Baseline Characteristics and Pruritus Stratification

	Placebo (n=15)	NGM282 0.3 mg (n=14)	NGM282 3.0 mg (n=16)	Total (n=45)
Age (mean years ± SD)	55.7 ± 12.7	56.6 ± 8.5	56.5 ± 9.8	56.2 ± 10.3
Gender (F/M)	13/2	13/1	15/1	41/4
Race (% White)	100%	100%	100%	100%
UDCA (mean mg/kg ± SD)	15.9 ± 3.5	15.2 ± 2.9	15.4 ± 5.0	15.5 ± 3.9
Pruritus at Baseline (n, %)	10 (66.7%)	9 (64.3%)	7 (53.8%)%	26 (61.9%)
Mild	4 (40.0%)	6 (66.7%)	2 (28.6%)	12 (46.2%)
Moderate	5 (50.0%)	2 (22.2%)	2 (28.6%)	9 (34.6%)
Severe	0	1 (11.1%)	3 (42.9%)	4 (15.4%)
Unbearable	1 (10.0%)	0	0	1 (3.8%)

Change in Pruritus Severity from Baseline to Day 28: VAS versus 5D Itch Scale

- Per protocol criteria for Baseline and Day 28 pruritus assessments were met by 38 subjects for VAS and 41 subjects for 5D Itch
- The was good agreement (k=0.56, p<0.0001) between the VAS and 5D Itch in measuring categorical change from Baseline in pruritus severity (Tables 2 and 3).
- There was no significant difference between the study arms in the categorical change by either VAS or 5D Itch (Table 2 and 3).
- There was no evidence of drug-induced pruritus in NGM282 treated subjects with VAS as measured by worsening or de-novo pruritus.
- Three NGM282 treated subjects developed de novo or worsening of pruritus during the study by 5D Itch versus 2 on placebo (Table 3):
  - Two 0.3 mg subjects had a past history of pruritus outside the 2 week prior to Baseline assessment window for the 5D Itch
  - A single 3 mg subject had a localized injection site reaction which was captured as generalized pruritus
- No subject was dose reduced or discontinued due to pruritus.

Table 2. Change in Pruritus Severity from Baseline to Day 28: VAS

	Placebo (n= 14)			NGM282 0.3 mg (n= 14)			NGM282 3.0 mg (n= 10)		
	Improve	No Δ	Worse	Improve	No Δ	Worse	Improve	No Δ	Worse
PRURITUS AT BASELINE	3	5	1	2	7	0	3	2	0
Mild	0	3	1	0	6	0	0	1	0
Moderate	2	2	0	1	1	0	0	1	0
Severe	0	0	0	1	0	0	3	0	0
Unbearable	1	0	0	0	0	0	0	0	0
NO PRURITUS AT BASELINE	0	5	0	0	5	0	0	5	0

Table 3. Change in Pruritus Severity from Baseline to Day 28: 5D Itch

	Placebo (n= 15)			NGM282 0.3 mg (n= 14)			NGM282 3.0 mg (n= 12)		
	Improve	No Δ	Worse	Improve	No Δ	Worse	Improve	No Δ	Worse
PRURITUS AT BASELINE	4	4	2	3	5	1	5	2	0
Mild	1	2	1	1	4	1	1	1	0
Moderate	2	2	1	1	1	0	1	1	0
Severe	0	0	0	1	0	0	3	0	0
Unbearable	1	0	0	0	0	0	0	0	0
NO PRURITUS AT BASELINE	0	5	0	0	4	1	0	4	1

Changes in Liver Chemistries: Correlation with Baseline Severity and Change in Pruritus

- Mean absolute ALP decreased in a significant, progressive, dose-dependent manner from Baseline to Day 28 in both active treatment arms, with greater decreases in the 3.0 mg arm (Table 4).
- There were also significant decreases from Baseline to Day 28 observed for ALT, AST and GGT.
- No significant decreases in direct or total bilirubin were observed due to the majority of subjects having normal levels at Baseline.

Table 4. Change in Liver Chemistries from Baseline to Day 28

Mean (SD)	Placebo (n=15)	NGM282 0.3 mg (n=14)	NGM282 3.0 mg (n=16)
ALP	3.9 (51.8)	-48.9 (55)*	-69.0 (66.5)*
ALT	1.3 (14.5)	-17.4 (13.5)*	-22.3 (26.6)*
AST	1.9 (9.9)	-11.1 (9.4)*	-12.0 (13.9)*
Direct Bilirubin	-0.00 (0.08)	-0.13 (0.44)	0.02 (0.19)
GGT	-5.6 (43.7)	-28.2 (48.7)*	-50.8 (71.9)*
Total Bilirubin	0.03 (0.13)	-0.15 (0.44)	-0.04 (0.22)
Total Bile Acids	4.3 (15.4)	-0.6 (36.6)	-22.6 (45.1)

* = p < 0.05

- Severity of pruritus at Baseline had a significant positive correlation with with all liver chemistry parameters, except GGT, with both the VAS and 5D Itch (Figures 1 and 2).
- However, there was no correlation between any of the liver parameters and change in pruritus from Baseline.
- The correlation with Baseline pruritus severity is consistent with other data where elevated liver enzymes are a surrogate for worse cholestasis and hepatobiliary injury, both of which are associated with a increased risk for pruritus.
- The discrepancy in the correlation data between Baseline severity and change in severity would suggest different independent mechanisms for triggering versus improvement or worsening of pruritus.

Figure 1.

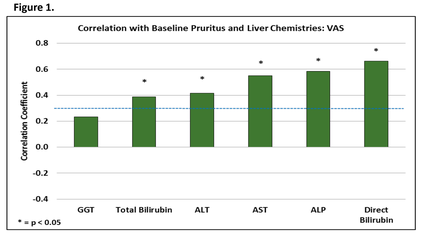
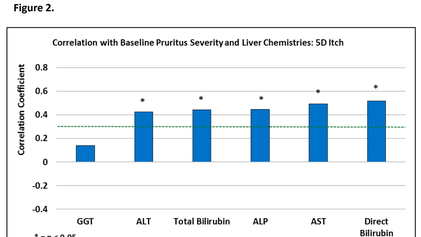


Figure 2.



Changes in Serum Bile Acids and Correlations with Baseline Severity and Change in Pruritus

- Dose dependent numeric decrease were observed in total BAs but did not reach statistical significance largely due to significant variability in individual patient baseline levels (Table 4).
- Similarly, decreases in the individual serum BAs were dose dependent and including those not directly impacted by the CYP7A1 pathway (Figure 3).
- The pattern of positive and negative correlation of serum BAs were relatively consistent between the VAS and 5D Itch as well as within each tool (Figures 4 – 7).
- Baseline severity VAS correlated positively with GCA, TCA, TCDCA, GCDCA, TUDCA and GUDCA and correlated negatively with DCA; this was generally aligned with the 5D Itch correlations (Figures 4 and 6).
- Change from Baseline in pruritus severity by VAS positively correlated with GCA whereas the 5D Itch was more broadly correlated with GCA, GCDCA and GUDCA (Figure 5 and 7).
- There was a positive correlation between GCA levels and both Baseline severity and change in severity of pruritus independent of measurement with the VAS or 5D Itch.
- DCA was negatively correlated with Baseline severity of pruritus and trended towards a negative correlation with change in severity of pruritus but did not reach statistical significance.

Figure 3. Change from Baseline to Day 28 of Absolute Concentrations on Individual Serum BAs

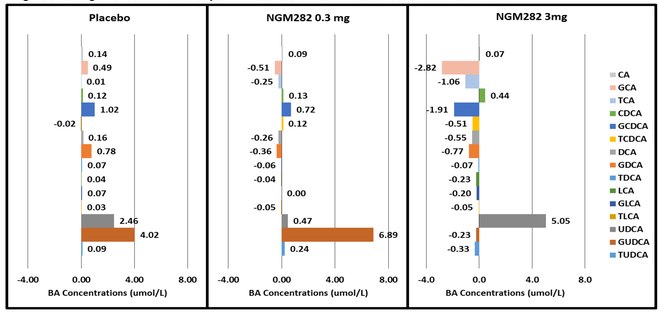


Figure 4.

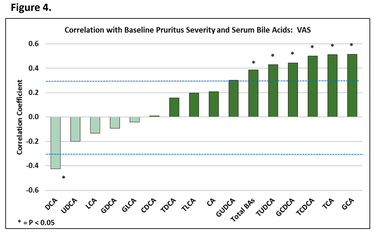


Figure 5.

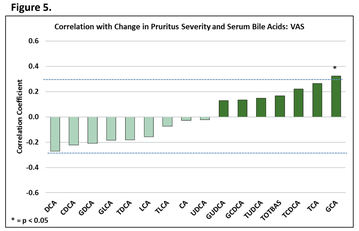


Figure 6.

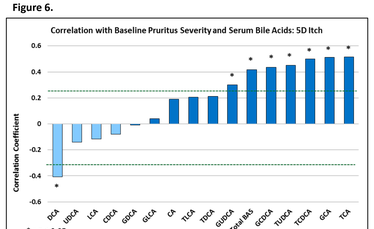
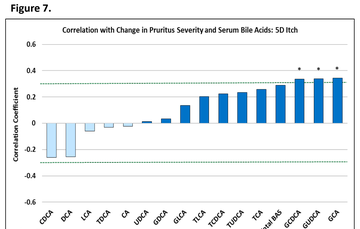


Figure 7.



DISCUSSION

- The pathogenesis of pruritus is poorly understood and the specific pruritogen(s) responsible for these symptoms remains largely unknown.
- Potential pruritogens appear to accumulate in the serum, are secreted into the bile, are biotransformed in the gut and the liver, and likely effect opiodergic and serotonergic pathways. [3]
- Although bile salts are pruritogenic, there is no correlation between pruritus severity and either degree of cholestasis or levels of serum or tissue BAs.
- Itch-specific neural pathways appear to be mediated through the Lysophosphatidic acid/Autotaxin (LPA/ATX) axis as well as by TGR5 receptors [3]
- Specific BAs excited into the small intestine may responsible for mediating the release of chemicals which directly modulate the LPA/ATX axis and/or TGR5 activation.[4]
- Patients with Alagille Syndrome treated with an ASBT inhibitor showed changes in serum BAs secondary to excretion of hepatic BAs into the gut may correlate with changes in pruritus severity.[5]
- Data with NGM282 may further support that changes in hepatic BA synthesis have differential effects on pruritus versus other therapies by altering the composition and amount of BAs excreted into the intestine thus altering the release of pruritogenic chemicals.

CONCLUSIONS

- There is good correlation between the VAS and 5D Itch measurements for severity of pruritus in patients with PBC, independent the visual (VAS) versus numeric (5D Itch) rating scale.
- Treatment with NGM282 is not associated with an increased incidence of drug-induced pruritus above that seen with placebo.
- Elevated liver chemistries are predictive of Baseline severity of pruritus but do not correlate with changes in severity over time.
- Changes in GCA levels may serve as a marker of pruritus severity as well as a biomarker of response to targeted treatments of pruritus.
- Further evaluation of these data are warranted to understand the role of specific BAs as biomarkers of changes in severity of pruritus for newer therapies specifically targeting BA synthesis

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