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TITLE: 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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PRESENTER: Marlyn Mayo

AUTHORS/INSTITUTIONS: M.J. Mayo , UT Southwestern, Dallas, Texas, UNITED STATES|A.J. Wigg, Flinders Medical Center, Adelaide, South Australia, AUSTRALIA|A.J. Thompson, St. Vincent's Hospital, Melbourne, Victoria, AUSTRALIA|S.K. Roberts, The Alfred Hospital, Melbourne, Victoria, AUSTRALIA|H. Arnold, Digestive Research Center, San Antonio, Texas, UNITED STATES|T.I. Hassanein, Southern California Liver research Center, Coronado, California, UNITED STATES|B.A. Leggett, Royal Brisbane and Women's Hospital, Brisbane, Queensland, AUSTRALIA|J.P. Bate, Royal Adelaide Hospital, Adelaide, South Australia, AUSTRALIA|M. Weltman, Nepean Hospital, Penrith, New South Wales, AUSTRALIA|E.J. Carey, Mayo Clinic Arizona, Scottsdale, Arizona, UNITED STATES|G. McCaughan, University of Sydney, Newtown, New South Wales, AUSTRALIA|S.J. Bollipo, John Hunter, New Lambton, New South Wales, AUSTRALIA|S.C. Gordon, Henry Ford Hospital, Detroit, Michigan, UNITED STATES|P.W. Angus, Austin Hospital, Heidelberg, Victoria, AUSTRALIA|S. Riordan, Prince of Wales Hospital, Sydney, New South Wales, AUSTRALIA|M.L. Shiffman, Liver Institute of Virginia, Richmond, Virginia, UNITED STATES|E. Young, Novotech, Sydney, New South Wales, AUSTRALIA|L. Ling, J. Luo, M. Elliott, S. Rossi, A.M. DePaoli, NGM Biopharmaceuticals, Inc., S. San Francisco, California, UNITED STATES|A.J. Muir, Duke University School of Medicine, Durham, North Carolina, UNITED STATES|

ABSTRACT BODY:

Abstract Body: Background: Pruritus (PRU) is a frequent comorbidity of primary biliary cirrhosis (PBC) which may be related to changes in bile acid (BA) metabolism. NGM282 is a novel engineered variant of FGF-19 that inhibits CYP7A1 and decreases both liver chemistries and serum BA in PBC patients. We evaluated the impact of NGM282 on PRU and correlations with liver chemistries and serum BAs. **Methods:** 45 subjects were randomized in a double blind fashion to NGM282 0.3 or 3mg vs placebo (PBO) SC for 28d with no exclusions for severity or treatment of PRU. Patients were stratified by presence of prurius (PRU) at BL using the 5-D Itch Scale (5D). PRU was measured by Visual Analogue Scale (VAS) and the 5D at BL and Days 14, 28 and 42. Subjects with a BL and Day 28 VAS (n=38) and/or 5D (n=41) were categorized as improved, no change or worsened based on a $\geq$20% change from BL at Day 28. Correlations between PRU and liver chemistries or serum BAs by VAS were assessed by Spearman correlation and regression analyses with a clinical anchor threshold of r $\geq$0.30 and $p<0.05$ as significant. Similar correlations for 5D used an ANOVA without adjustment. **Results:** BL PRU was seen in 54%, 64% and 67% of the PBO, 0.3mg and 3mg arms, respectively. There was significant agreement ($k=0.56$, $p<0.0001$) between the VAS and 5D in measuring categorical change from BL in PRU severity, but no significant difference between the study arms in the categorical change by either scale (Table 1). Only 3 subjects developed de novo or increased PRU during the study, and only by the 5D.. Both 0.3mg subjects had a past history of PRU prior to BL, and the 3mg subject had PRU only at the injection site. No subject was dose reduced or discontinued due to PRU. Severity at BL by VAS and 5D correlated positively with direct bilirubin, ALP, AST and ALT. BL severity by VAS also correlated positively with GCA, TCA, TCDCA, GCDCA, TUDCA and GUDCA, but correlated negatively with DCA. Change from BL severity at Day 28 by VAS positively correlated positively with GCA. The 5D was positively correlated with serum BAs for both BL severity and change from BL severity but only partially aligned with the VAS. **Conclusions:** No clinically significant evidence of drug-induced PRU was seen in NGM282 and specific BAs may serve as possible biomarkers for monitoring changes in PRU severity. These data warrant further evaluation in larger populations of cholestatic patients.

TABLE TITLE: Table 1

Table 1									
.	PBO			0.3mg			3mg		
.	Improve	No Δ	Worsen	Improve	No Δ	Worsen	Improve	No Δ	Worsen
VAS: BL PRU	3	5	1	2	7	0	3	2	0
VAS: No BL PRU	-	5	0	-	5	0	-	5	0
5D: BL PRU	4	4	2	3	5	1	5	2	0
5D: No BL PRU	-	5	0	-	4	1	-	4	1