Effect of NGM282, an FGF19 Analogue, on Pruritus in Patients with Primary Sclerosing Cholangitis: Analysis of a Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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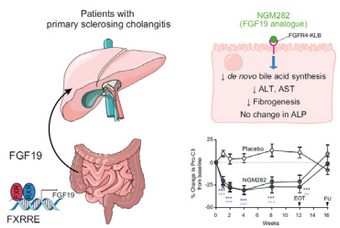
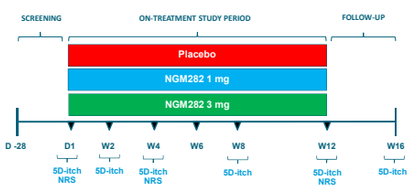
BACKGROUND AND AIMS

- NGM282 is an engineered, non-tumorigenic analogue of human FGF19 [1-2]
- Administration of NGM282 resulted in improvements in ALT, AST, and serum markers of fibrogenesis (ELF and Pro-C3), without reducing alkaline phosphatase (ALP), in 12 weeks in patients with primary sclerosing cholangitis (PSC) [3]
- Approximately 50% of PSC patients experience pruritus, a symptom that can reduce quality of life; however, several drugs in development for PSC further increased pruritus [4-5]
- We report here the effect of NGM282 on pruritus after 12 weeks of treatment



METHODS

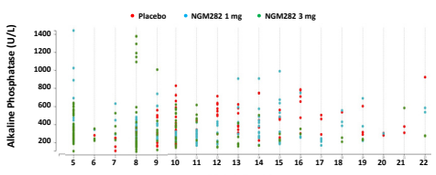
- Sixty-two PSC patients received NGM282 1 mg (n=21), 3 mg (n=21) or placebo (n=20) once daily for 12 weeks, with a follow-up visit at week 16 [3]
- Key inclusion criteria included PSC by EASL criteria and an elevated ALP>1.5xULN
- The primary endpoint was the change in ALP from baseline (BL) to Week 12 (W12)
- 5D-itch pruritus questionnaires (scores range from 5 to 25, with higher scores indicating worse itch) were collected
- Patients also recorded pruritus intensity on a numeric rating scale (NRS) ranging from 0 to 10, with higher numbers indicating more severe itch
- An analysis of covariance (ANCOVA) model was used to compare the NGM282 groups with the placebo group

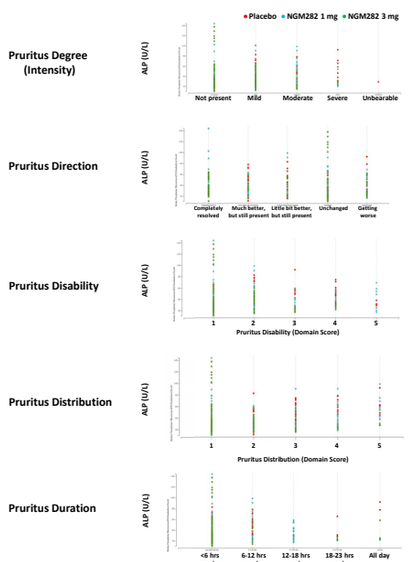


RESULTS

- We evaluated pruritus using the 5D-itch scale, a multidimensional measure of itching that has been validated in patients with chronic pruritus [6]
  - Domains include pruritus degree, direction, disability, distribution and duration
- We assessed correlation between pruritus and ALP, a marker of cholestasis and an endpoint in almost all PSC trials to-date, using linear regression
- We found that levels of ALP did not correlate with 5D-itch total score or its five domains

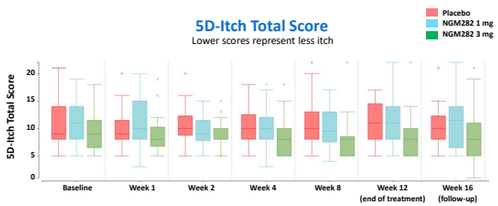
Lack of Correlation between ALP and 5D-Itch Score and Domains



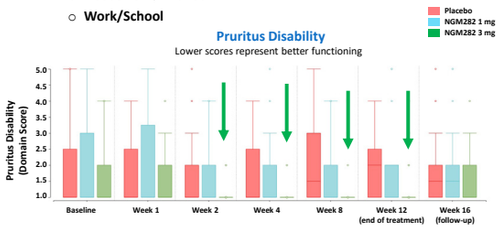


Effect of NGM282 on 5D-Itch Scale

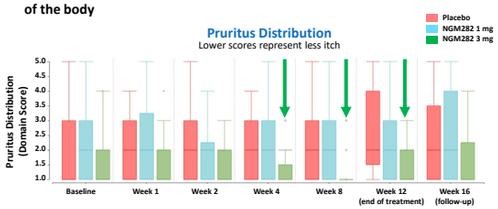
- 5D-itch scale has been demonstrated to be able to detect changes over time, representing a useful outcome measure in clinical trials [6]
- At week 12, placebo-adjusted mean changes in 5D-itch score were −0.50 (95%CI, −3.17 to 2.17) and −1.60 (−4.30 to 1.10) in the NGM282 1 mg and 3 mg groups, respectively, suggesting a trend of improvement with NGM282 therapy



- In particular, patients treated with NGM282 3 mg showed a trend of improvement in pruritus disability domain score as early as Week 2, and at repeated assessments at Weeks 4, 8 and 12 (end of treatment)
  - Pruritus disability domain assess the impact of pruritus on the following activities
    - Sleep
    - Leisure/Social
    - Housework/Errands
    - Work/School

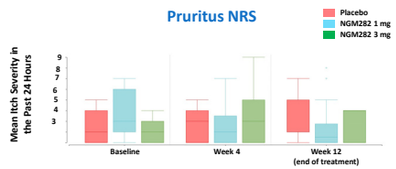


- Patients treated with NGM282 3 mg showed a trend of improvement in pruritus distribution, which assess the location of pruritus in various parts of the body



Effect of NGM282 on NRS

- The pruritus NRS is a patient-reported measure that assesses maximum itch intensity in the previous 24 hours using a point scale of 0 to 10. These daily reports were averaged for each study week to produce a weekly NRS score
- At week 12, placebo-adjusted mean changes in pruritus NRS were −0.47 (−1.93 to 0.99) and −0.52 (−1.96 to 0.92) in the NGM282 1 mg and 3 mg groups, respectively



- Changes from baseline to week 12 in pruritus NRS correlate with changes in pruritus degree (r=0.43, p<0.01), pruritus direction (r=0.43, p<0.01), pruritus disability (r=0.30, p<0.05) and pruritus distribution (r=0.33, p<0.5), but not pruritus duration, from the 5D-itch scale

Correlation with ELF

- ELF score, a composite panel of 3 components of fibrogenesis and matrix remodeling (the N-terminal pro-peptide of type III collagen [PIIINP], the tissue inhibitor of metalloproteinase 1 [TIMP-1] and hyaluronic acid [HA]), has been demonstrated to be a strong predictor of transplant-free survival in patients with PSC [7-8]
- A change in ELF score of −0.19 from baseline to week 12 has been shown to predict survival free of PSC-related clinical events, such as ascites, encephalopathy, variceal hemorrhage, cholangiocarcinomas, jaundice, liver transplant or death [9]
- NGM282 reduced ELF (−0.29 and −0.37 from baseline to week 12 for 1 mg and 3 mg, respectively), with the most pronounced improvement in patients who had an advanced stage of disease (−0.52 and −0.58 from baseline to week 12 for 1 mg and 3 mg, respectively, in patients with baseline ELF >9.8) [3]

Correlation Between Change in 5D-Itch Domains and Change in ELF

Change from Baseline to Week 12	Δ Degree	Δ Direction	Δ Disability	Δ Distribution	Δ Duration
Δ ELF	0.14	0.23	0.21	0.19	0.02
Δ PIIINP	**0.26***	**0.27***	0.24	**0.42*****	0.16
Δ TIMP-1	0.13	0.24	0.23	0.22	−0.03
Δ HA	0.06	0.06	0.08	−0.05	−0.13

Shown are correlation coefficient. ***p<0.001, **p<0.01, *p<0.05

- Changes from baseline to week 12 in PIIINP, but not TIMP-1 or HA, correlate with changes in pruritus distribution, degree and direction

Summary

	PBO (n = 20)	NGM282 1mg (n = 21)	NGM282 3mg (n = 21)
5D-Itch Scale			
5D-Itch Score (BL)	10.70 (4.60)	11.14 (3.79)	9.50 (3.87)
Change in 5D-Itch Score from BL to W12, LS mean	0.60	0.30	−1.52
P value (W12 vs BL)	0.45	0.70	0.06
NGM282 vs Placebo, difference between means (95% CI)		−0.50 (−3.17 to 2.17)	−1.60 (−4.30 to 1.10)
P value (NGM282 vs Placebo)		0.78	0.06
Numeric Rating Scale			
Pruritus NRS (BL)	1.50 (1.79)	2.29 (2.35)	0.90 (1.25)
Change in Pruritus NRS from BL to W12 , LS mean	0.36	0.01	−0.32
P value (W12 vs BL)	0.38	0.98	0.48
NGM282 vs Placebo, difference between means (95% CI)		−0.47 (−1.93 to 0.99)	−0.52 (−1.96 to 0.92)
P value (NGM282 vs Placebo)		0.60	0.56

CONCLUSION

- In this population of patients with PSC, treatment with NGM282 was not associated with drug-induced pruritus, but was associated with a trend of improvement in pruritus, especially in the 3 mg group
- Levels of ALP did not correlate with 5D-itch total score or its five domains
- Changes from baseline to week 12 in PIIINP correlate with changes in pruritus distribution, degree and direction, revealing an unexpected connection between collagen turnover and pruritus
- These patient experience data may provide important additional information about the clinical benefit of NGM282
- Clinically relevant, patient-reported outcome measures should be evaluated in future PSC trials

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References:

1. *Zhou et al., Cancer Res 2014; 74:3306-3316*
2. *Luo et al., Sci Transl Med 2014; 6:247ra100*
3. *Hirschfield et al. J Hepatol 2019;70:483-493*
4. *Kowdley et al., AASLD 2017*
5. *Patel et al., AASLD 2018*
6. *Elman et al., Br J Dermatol 2010;162:587-593*
7. *de Vries et al., Liver Int 2017;37:1554-1561*
8. *Vesterhus et al., Hepatology 2015;62:188-197*
9. *Muir et al., Hepatology 2019;69:684-698*

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Author disclosures on file at EASL 2019