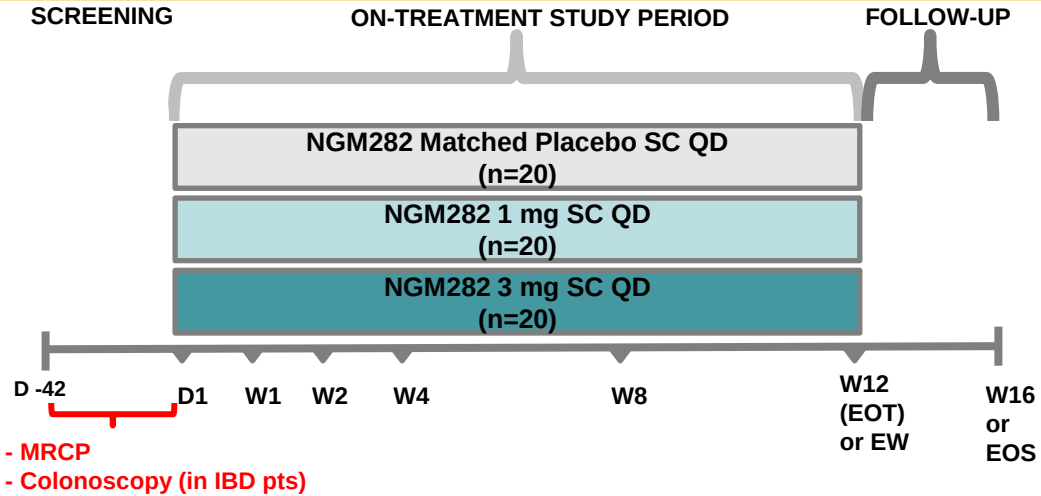
NGM282 Phase 2a Study in PSC: Overview of Study Design



- Proof of concept study to evaluate safety, biologic activity and PK
- Primary endpoint was change in ALP from baseline
- Stratified by UDCA use at Baseline
- 35 sites in the US, Netherlands, UK and France
- 95 subjects screened
  - 62 subjects randomized and treated
  - 33 screen failures (35% screen failure rate)
- First patient enrolled March 2016, last patient enrolled Feb 2017 (~10.5m)

Key Considerations in Developing I/E Criteria for NGM282 PSC Phase 2a Study

- Goal was to include a broad range of subjects, including those traditionally excluded from trials
- Established safety up to 1 year in PBC (n=35) and up to 12 weeks in NASH (n=150)
- No metabolic liability in terms of drug interactions or PK
- Mechanism of action focused on decreased toxic bile acid synthesis not immunologic or anti-inflammatory
  - Minimal limitations on acceptable concomitant medications for common comorbid conditions
- Regional differences in UDCA use

NGM282 Phase 2a Study in PSC: Development of Enrollment Criteria

- PSC Experts
  - Ulrich Beuers
  - Gideon Hirschfield
  - Peter Jansen
  - Marlyn Mayo
- Patient representatives
  - Ricky Safer
  - Rachel Gomel
- DSMB Co-Chairs approved any amendments to criteria
  - Elizabeth Carey
  - Peter Jansen

NGM282 Phase 2a Study in PSC: Inclusion Criteria - Diagnosis and Medical

- Confirmed diagnosis of PSC based any two of the following three criteria:
  - Historical evidence of an elevated ALP > ULN
  - Abnormal cholangiography consistent with PSC as measured by MRCP, ERCP or PTC
  - Liver biopsy consistent with PSC
    - Small duct PSC on liver biopsy must also have a concurrent diagnosis of IBD
- Patients with a dominant stricture with no evidence of cholangiocarcinoma and/or stricture will not result in significant fluctuations in ALP
  - MRCP in all patients during Screening to rule out above issues
  - Total bilirubin ≤ 2.5 mg/dL for 6 months prior to Screening (only in patients with a dominant stricture)
- Patients with IBD with the following criteria:
  - Colonoscopy within 12 months of Screening with no evidence of dysplasia
  - No episode of an IBD flare or flare-related bloody diarrhea within 6 months of Screening and through Day 1
  - Stable doses of biologics, immunosuppressive, or corticosteroids for ≥ 12 weeks prior to Screening and through Day 1
    - Vedolizumab is an excluded biologic

NGM282 Phase 2a Study in PSC: Inclusion Criteria - Laboratory

- Patients must have the following additional laboratory parameters at Screening:
  - ALP > 1.5 × ULN (*173 IU/L by Central Lab*)
  - Total bilirubin ≤ 2.5 mg/dL
  - ALT/AST < 5 × ULN
  - Serum creatinine < 2 mg/dL or creatinine clearance > 60 mL/min by Cockroft-Gault calculation
  - Platelets > 100 K/uL
  - INR ≤ 1.3 (in the absence of anticoagulant therapy)
  - Carbohydrate antigen 19-9 (CA19-9) ≤ 130 U/mL
    - Patients with a CA 19-9 > 130 U/mL but <300 U/L may be enrolled if
      - Two historical results within a year of screening that are a minimum of 4 weeks but not greater than 1 year apart within
      - Not more than 50 U/mL difference between the two results

NGM282 Phase 2a Study in PSC: Inclusion Criteria – UDCA Dosing

- Patients taking UDCA will be allowed to enroll if meeting the following criteria:
  - Total daily dose of < 27 mg/kg/day for a minimum of 12 weeks
  - No significant dosage changes during 8 weeks prior to Screening
  - Minimum of 12 week washout period prior to Screening if UDCA is stopped
  - UDCA **must** not be started during study period
- **Patients will be stratified by UDCA or no UDCA use at Baseline**

NGM282 Phase 2a Study in PSC: Exclusion Criteria – PSC Related

- Acute or chronic liver disease of an etiology other than PSC
  - Patients with stable treated overlapping PSC and autoimmune hepatitis will be allowed to enroll
  - Minimum 12 weeks of immunosuppression with no hepatic flare during that time period
- Secondary or IgG4-related sclerosing cholangitis
- Dominant stricture of clinical concern on MRCP at Screening
- Placement of a bile duct stent or percutaneous bile duct drain within 3 months of Screening
  - Patients who have undergone balloon dilation will be allowed into the study after a minimum of 4 weeks post-procedure
- History, evidence, or high suspicion of cholangiocarcinoma or other hepatobiliary malignancy
- Acute cholangitis within 12 weeks of Screening up to Day 1 as defined by clinical symptoms (fever, abdominal pain) and elevated WBC count
  - Chronic preventative antibiotic use is permitted
  - Presumptive antibiotics use is permitted if outside 12 week window

NGM282 Phase 2a Study in PSC: Exclusion Criteria – Medical

- Evidence or history of decompensated cirrhosis (Childs Class B or C) as defined by clinical, laboratory or histologic assessments
  - **Patients with compensated cirrhosis are allowed to enroll into the study**
  - Patients with pre-sinusoidal esophageal varices with no history or evidence of bleeding may be enrolled as long as there is no evidence of hepatic decompensation.
- Prior liver transplantation or on the transplant waiting list
- Any contraindication or inability to obtain a screening MRCP or colonoscopy
- Clinically significant abnormal ECG
- HBV, HCV, HIV infection
- History of malignancy diagnosed or treated within 2 years of Screening
  - Recent localized treatment of squamous or non-invasive basal cell skin cancers are permitted
  - Cervical carcinoma in situ is allowed if treated prior to Screening
  - Subjects under evaluation for malignancy are not eligible

NGM282 Phase 2a Study in PSC: Prohibited Medications

- New prescription/OTC medications or regimen changes of existing therapies from 4 weeks prior to Day 1 **should** be avoided
- Investigational agents or devices for any indication
- Agents used for the treatment of any condition listed in the exclusionary enrollment criteria
- Off-label use of therapies for PSC such as oral vancomycin or other antibiotics (for PSC only), vedolizumab within 12 weeks of Screening through the EOS visit
- Known hepatotoxic agents
- Agents which can increase or decrease ALP
  - *Concomitant medications can be screened at* ***http://livertox.nih.gov***
  - Patients on stable doses of medication for a minimum of 12 weeks can be considered for enrollment
- Any herbal medications other than standard vitamin supplements

NGM282 Phase 2a Study in PSC: Reasons for Pre-Screening and Screen Failures

- Primary reasons for pre-screening failures
  - Low ALP (>70%)
  - Changes in IBD treatment
  - Decompensated cirrhosis and/or on transplant list
  - Vedolizumab use (predominantly US)
  - Recent stent placement or ballooning
  - Acute cholangitis
- Primary reason for screen failures (n=33)
  - Low ALP = 14
  - Low ALP plus other lab = 7
  - Dominant stricture with unstable ALP and/or bilirubin = 3
  - Acute cholangitis during screening = 2
  - Elevated CA19-9 = 2
  - Platelet < 100 K/Decompensated cirrhosis = 1
  - Suspected cholangiocarcinoma =1
  - Secondary sclerosing cholangitis = 1
  - Change in IBD therapy based on symptoms and screening colonoscopy = 1
  - Positive drug screen (non-THC) =1