Academic perspectives on trials

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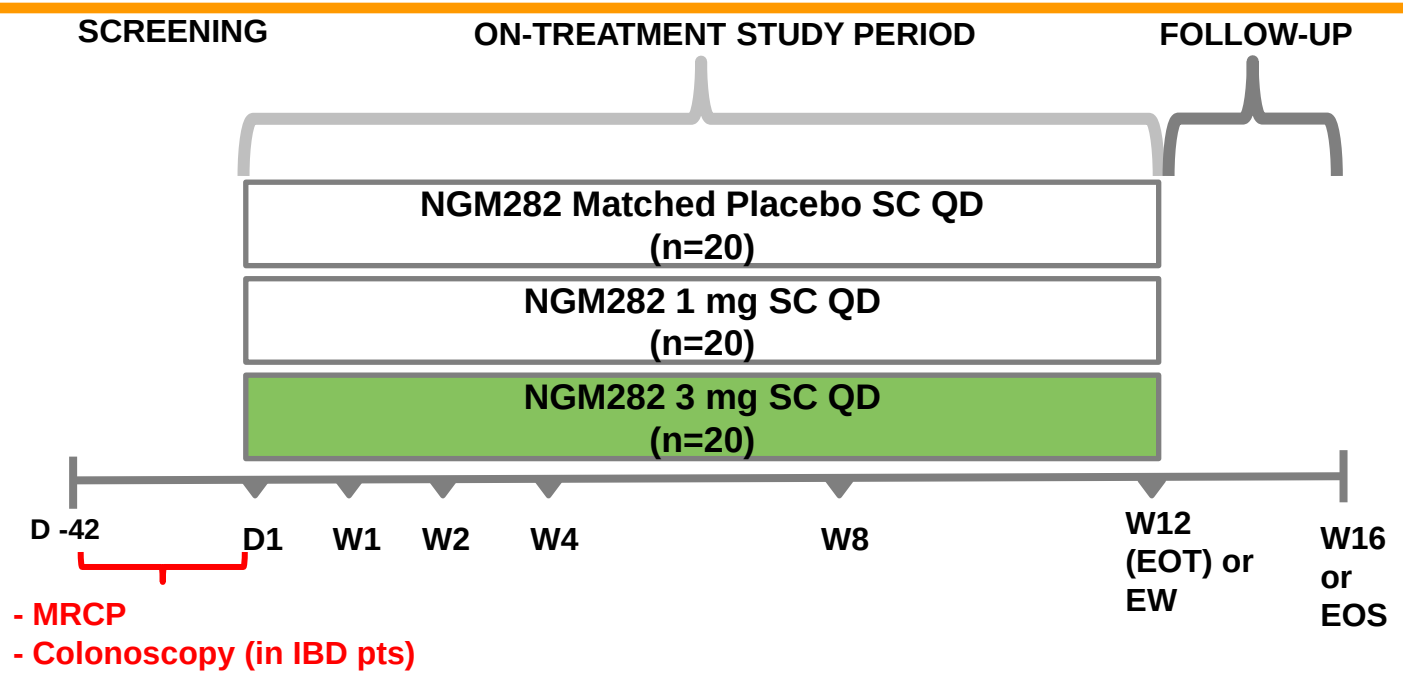
It is hard!

- Investigator initiated
- Industry sponsored
- Observational and Interventional

Patient Recruitment, Retention, Eligibility and Screen Failure Rates in clinical trials

- Recruitment
  - Dedicated clinic and dedicated programme
  - Upfront from first visit
  - Challenges: University, Family, Work
- Retention
  - Generally not an issue but frequency of visits is a burden
- Eligibility
  - ALP, ALP, ALP
  - Colonoscopy
  - Dysplasia
  - Cirrhosis
- Screen failure
  - ALP, ALP,ALP
  - Cirrhosis
  - Cholangitis

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: 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
- Other screening laboratory values will be reviewed by Medical Monitor as indicators of other medical exclusionary criteria

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: 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