PSC Project and working group updates

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PSC Inclusion/ Exclusion Criteria Working Group

- **Goal:**
  - examine inclusion/ exclusion criteria for PSC clinical trials
  - consider the evidence in support of inclusion/ exclusion criteria
  - recommend standardized criteria when appropriate

INTERCEPT: Study Inclusion/Exclusion Criteria

Population
- PSC specific considerations
  - UDCA
  - IBD (+medications)
  - Diagnosis/Secondary cholangitis

Endpoint
- Population enrichment
  - Biochemistry?
  - Outcomes?
- Intended indication/relevance

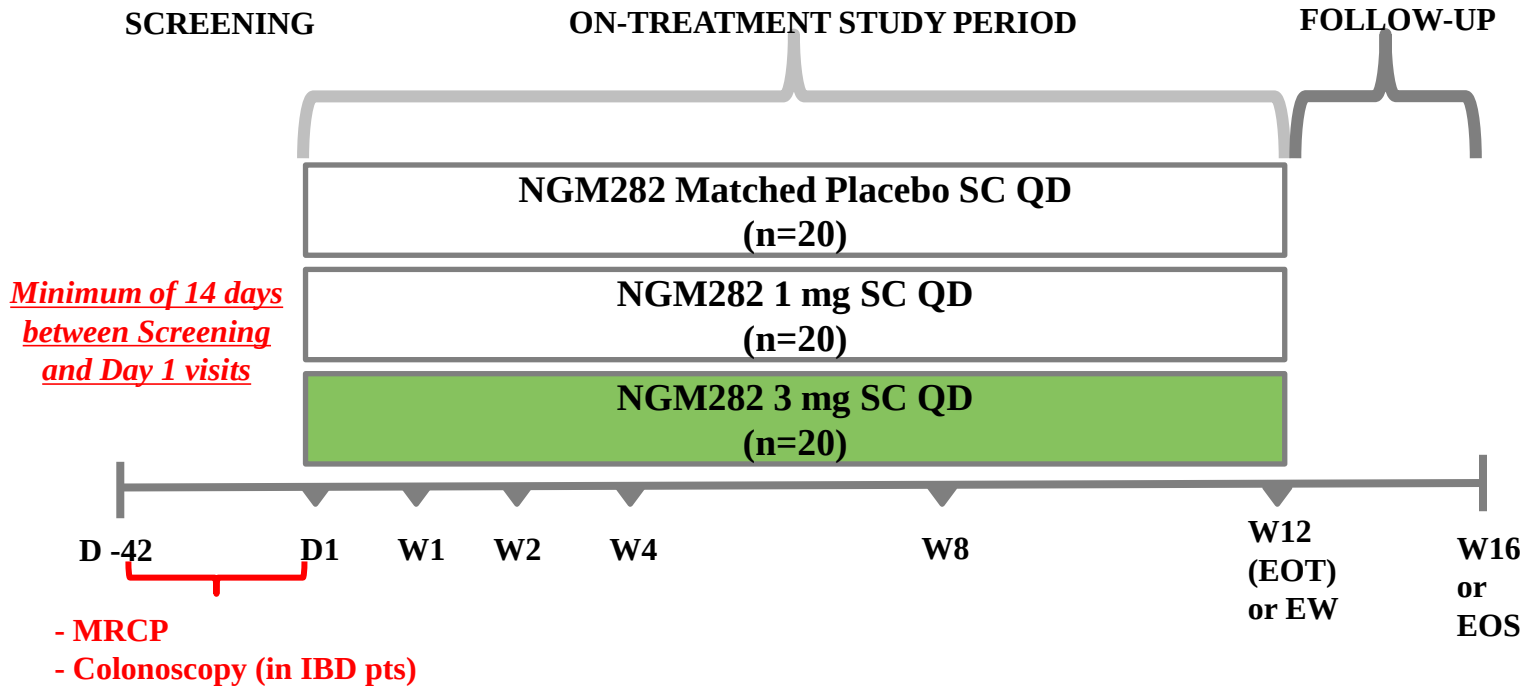
Investigational treatment
- Mechanism of action
- Drug-specific considerations or limitations

c/o Intercept Pharma

PSC Specific Considerations

- **Orphan population**
  - Selecting appropriate endpoints and populations which will still allow for practical trial enrollment
- **Co-morbidities**
  - Include or exclude?
  - Severity?
  - Clarity to assess the study endpoint may limit applicability of results?
- **UDCA treatment**
  - Not approved but commonly used
- **Strictures**
- **Cholangiocarcinoma**

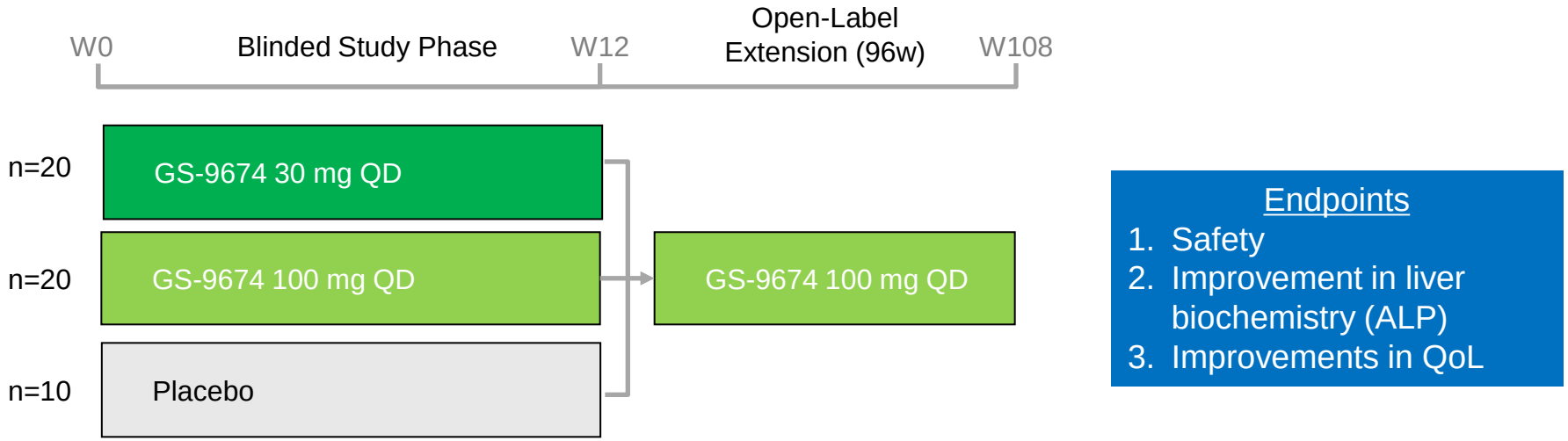
NGM282 Phase 2a Study in PSC: Overview of Study Design



- 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)

c/o NGM

GS-9674 for PSC: Phase 2 Study Design



Endpoints

1. Safety
2. Improvement in liver biochemistry (ALP)
3. Improvements in QoL

Purpose: To determine the safety, tolerability, and efficacy of GS-9674 in patients with PSC.

Population: Non-cirrhotic PSC (cholangiography)
ALP >1.67x ULN

IPSCSG

- Host centre: Amsterdam
- Academic lead (Beuers/Poinsioen)
- Working groups: clinical, cancer, definitions

IPSCSG Definitions

- Delphi process
- Ongoing
- Goal is a manuscript that is a “goto” manual for PSC definitions and that aligns with forum, including working group on trial design

IPSCSG Definitions Paper Outline

Introduction and unmet need

Methodology

Delphi process

Diagnosis

- **Clinical presentation**
- **Laboratory markers**
- **Imaging incl. dominant stricture**
- **Pathology**
- **Exclusion of secondary sclerosing cholangitis**

IBD

Phenotypes-

- **Classical**
- **Small duct**
- **Overlap**
- **Paediatric - Mark**
- **PSC no IBD**

Staging of liver disease

Clinical endpoints

Liver transplant, liver related death, cholangitis, cirrhosis, cholangiocarcinoma, CRC

Symptoms

Post-transplant recurrence

Definitions in Context of clinical practice and trials (gaps and opportunities)

Example

Cholestasis is a defining features of primary sclerosing cholangitis and in reaching a diagnosis for inclusion in clinical trials, the expectation should be that the majority of patients will have evidence of an abnormal serum liver test profile for more than 6 months

In patients with PSC a combination of serum liver tests and simple clinical parameters, has the ability to define those patients at greater or lower risk of disease progression, and can be used to define risk strata for trial purposes.

For patients with normal serum liver tests, the definition of PSC requires a convincing cholangiopathy evident by either imaging or histology

Serologic testing for ANCA reactivity should not be used as a disease defining test.

Serum levels of CA19.9 whilst sensitive for biliary inflammation and malignancy, cannot be used alone to define the presence of cholangiocarcinoma.

Serum markers of liver fibrosis are associated with underlying liver disease severity across liver diseases, and can be used to define the risk of disease-associated events.

Serum IgG4 concentrations cannot be used to define absolutely a sub-group of patients with different clinical course in PSC.

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Discussion

Berkeley School of Public Health