1. Executive Summary & Key Messages

Indication: Liver-E
Modality: siRNA therapy
Formulation/Route: prefilled syringe / subcutaneous
Planned regimen (synthetic): 100 mg Q4W

Key messages:
- Hepatrel is being developed for Liver-E.
- Primary endpoint: Mean change in Composite Index at Week 24.
- Primary result: LS mean difference -1.11 (Drug – Placebo), p=0.016.
- Safety: common AEs include Arthralgia, Rash, Elevated ALT.

2. Background & Unmet Need

Liver-E is associated with persistent symptoms and variable response to standard therapy.
This synthetic briefing book is structured to support retrieval-augmented generation (RAG) practice.

Document governance (synthetic):
- Document version: v1.8
- Program identifier: AMGN-D008-401
- Intended use: internal training / prototype only

3. Mechanism of Action

Proposed mechanism: gene expression silencer.
MOA summary: Reduces target mRNA to decrease protein expression.

Biology notes (synthetic):
- Target pathway is assumed disease-relevant for training purposes.
- Biomarker shifts are described as supportive evidence in later pages.

4. Study Design

Trial: AMGN-D008-401 (Phase 2), randomized, double-blind, placebo-controlled (synthetic).
Population: Adults with moderate-to-severe Liver-E with inadequate response to standard therapy.

Arms:
- Arm: Hepatrel 100 mg Q4W, n=237
- Arm: Placebo, n=208

Key inclusion criteria:
- Confirmed diagnosis per protocol definition
- Baseline disease activity above threshold
- Stable background therapy for ≥4 weeks

Key exclusion criteria:
- Severe uncontrolled comorbidity (per protocol)
- Recent major surgery within 12 weeks
- Known hypersensitivity to components

5. Endpoints & Analysis Overview

Primary endpoint: Mean change in Composite Index at Week 24
Secondary endpoint: Durable response at Week 24

Analysis notes (synthetic):
- Primary analysis uses an intention-to-treat estimand.
- Missing data handled via multiple imputation (illustrative).
- Multiplicity control via hierarchical testing (illustrative).

6. Efficacy Results

Primary outcome:
- Result: LS mean difference -1.11 (Drug – Placebo)
- 95% CI: [-1.51, -0.71]
- p-value: 0.016

Secondary outcome:
- Interpretation: Numerically favored active arm; supportive trend

Discontinuations:
- Overall discontinuation rate (synthetic): 4.6%

7. Safety Summary (TEAEs)

Safety overview (synthetic):
- Serious AE rate: 3.4%
- Discontinuation due to AE: 3.4%

Common adverse events listed below.

Common TEAEs (synthetic)

Adverse Event	Rate (%)
Arthralgia	9.5
Rash	7.6
Elevated ALT	6.1
Diarrhea	4.9
Upper respiratory infection	3.0
Injection-site reaction	2.0

8. Dosing & Administration

Route: subcutaneous
Formulation: prefilled syringe
Regimen: 100 mg Q4W

Administration notes (synthetic):
- Missed dose: take as soon as remembered unless near next scheduled dose.
- Storage: controlled room temperature unless specified otherwise.
- Concomitant therapy: per protocol allowances.

9. Contraindications, Warnings & Monitoring

Contraindications:
- Known hypersensitivity to active substance or excipients.

Warnings/Precautions:
- Monitor for hypersensitivity reactions.
- Assess for infection risk in susceptible patients.
- Consider hepatic monitoring if clinically indicated.

Monitoring recommendations (synthetic):
- Baseline labs per protocol (CBC, CMP)
- Periodic assessment of liver enzymes
- Clinical monitoring for infections

10. Appendix: Abbreviations & Traceability

Abbreviations:
- AE: Adverse event
- SAE: Serious adverse event
- TEAE: Treatment-emergent adverse event
- ITT: Intention-to-treat

Traceability fields (synthetic):
- Drug ID: D008
- Trial ID: AMGN-D008-401
- Document version: v1.8
- Date: 2025-12-26

Note: This document is synthetic and intended only for RAG/agent practice.