INVESTIGATION OF DEEP B-CELL DEPLETION FOR IMMUNE RESET: TRIAL DESIGN CONSIDERATIONS

HEALTHY VOLUNTEERS VS PATIENTS IN EARLY-PHASE B-CELL THERAPY STUDIES

For *in vivo* CAR-T and T-cell engagers, one of the earliest and most important study design decisions is whether to begin in healthy volunteers or in patients.

SAFETY CONSIDERATIONS

Start in Healthy Volunteers

To generate human clinical pharmacology data and characterize B-cell depletion and recovery kinetics.

Suitable for investigational products with low risk of cytokine release syndrome (CRS).

OR

Start in Patients

When premedication to reduce the potential incidence or severity of CRS is a consideration, and when early efficacy is needed.

Starting doses will be subtherapeutic, with limited potential for early Pharmacodynamics (PD) and efficacy readouts.

Healthy Volunteers vs Patients

Healthy Volunteers (HV)

Speed and Data Clarity

Pros

- Faster recruitment
- Access to large volunteer databases
- Cleaner Pharmacokinetics(PK)/ Pharmacodynamics (PD) signals
- Earlier dose de-risking
- Helps identify biologically active dose ranges
- May reduce exposure of rare patients to subtherapeutic doses

Cons

- Vaccination restrictions
- Limited dosing duration in some settings

Best used when: dose-depletion behavior is the key question

Patients

Earlier Biological and Clinical Insight

Pros

- Earlier efficacy signal
- Disease-relevant biological context
- Tissue-level validation
- Supports basket disease indication studies
- Disease indication-specific data for B-cell depletion kinetics

Cons

- Disease indication recruitment rate is typically lower than for HVs
- Prior treatment failure often required
- Heterogeneous outcome measures
- Greater biological variability
- More operational complexity and potentially longer duration of trial

Best used when: biological relevance or early efficacy is the key question

Data-Led Pivot from HVs to Patients

HVs → Example pivot criterion: **Peripheral blood B-cell suppression sustained for < 2 months** *Pivot should be data-led, not date-led* → **Patients**

Prepare ethics and patient-site readiness in advance

Plan governance before the pivot is needed

Operational Enablers

Rapid Biomarker Turnaround	Safety Monitoring Priorities	Adaptive Study Execution
TBNK flow cytometry on live whole blood should be processed rapidly—ideally within 24 hours, no later than 72 hours—to inform dose escalation, safety review, depletion depth, nadir timing, and early recovery kinetics.	Treat CRS as an early monitoring priority. Watch for fever, malaise, shortness of breath, cardiovascular changes, subtle ICANS-like neurologic signs, and viral reactivation risk.	Successful studies depend on flexible protocols, rapid safety review, pre-planned cohort transitions, and close coordination between the site, CRO, sponsor, and lab.

Examples of patient cohorts/basket indications

Systemic Lupus Erythematosus (SLE)	Rheumatoid Arthritis (RA)	IgA nephropathy (IgAN)	Idiopathic inflammatory myopathies	Scleroderma

Sponsor takeaway: Programs move most efficiently when recruitment strategy, safety monitoring, biomarker logistics, and pivot planning are aligned from the outset.