Toxicology

Early Safety Studies

In vitro and silico safety screening studies of potential candidates have been conducted to uncover any potential safety alerts that can be an indication of potential functional consequences resulting from activation or inhibition of critical targets, usually off-target effects.

The list of the completed studies is as follows:

- Leadscope Cerep Panlab screen (nonGLP)
  - At least 44 targets
- SAR alerts (in silico, nonGLP)
  - Safety predictions based on chemical structure and any published known activity towards key targets in cardiovascular, reproductive, developmental, gene, hepatobiliary, urinary tract, neurological and carcinogenic toxicities
- Written assessment of abuse liability
  - Primarily for CNS-active moieties, which does not currently seem to be the case for any compounds screened to date
- Mini Ames (nonGLP)
  - In vitro prediction of mutagenicity, which may be predictive of carcinogenicity in humans
- hERG (nonGLP)
  - In vitro prediction of hERG channel interaction/inhibition, which may be predictive of QT interval perturbations/arrhythmias
- Oral single dose MTD in C57BL/6 mice (nonGLP)
- Oral repeat dose DRF in C57BL/6 mice (nonGLP)
- Oral single dose MTD in NHPs (nonGLP)

Planned IND-enabling Safety Studies

Below is the list of the planned studies (including supporting rationale), directed by known and anticipated biologic responses, as well as by world-wide regulatory guidance related to safety studies in animals.

- Stability/homogeneity dosing solutions (GLP/GMP API)
  - Required to support dosing concentrations in GLP studies
- Oral repeat dose in rats (nonGLP)
  - Better recognized tox species, larger animal for greater availability and access to important tissues
  - Key species for IND- and Registration-enabling GLP toxicology
  - Duration of study may change to 14 days based on any potential findings from a 21-day mouse study
- Oral Respiratory rat study (GLP)
  - 100, 300, 600 mg/kg oral, will be based on MTD in rodents
  - Most recognized species for pulmonary safety assessments
  - A required study for patient safety pharmacology
- Oral Cardiovascular NHP study (GLP)
  - 100, 300, 600 mg/kg, oral, will be based on MTD in NHPs
  - Essential to use nonrodent model due to differences in ion channels between rodents and humans
  - A required study for patient safety pharmacology
- Oral CNS rat study (GLP)
  - 100, 300, 600 mg/kg, oral, will be based on MTD in rodents
  - Most recognized species for CNS assessments
  - A required study for patient safety pharmacology
- hERG (GLP)
  - Required, as described earlier
- Ames (GLP)
  - Required, as described earlier
- Oral Mouse lymphoma assay (GLP)
  - Required to as part of carcinogenicity assessment
  - Dose levels based on rodent studies
- Oral Rat micronucleus study (GLP)
  - Required to as part of carcinogenicity assessment
  - Dose levels based on rodent studies
- 28-day repeat dose in rats (GLP)
  - Required to support the planned clinical study, match or exceed dose levels (exposure), frequency and duration
  - 30, 60, 100 mg/kg, oral, will be based on 14-day repeat dose study in rodents
- 28-day repeat dose in NHP (GLP)
  - Required to support the planned clinical study, match or exceed dose levels (exposure), frequency and duration
  - 30, 60, 100 mg/kg, oral, will be based on 14-day repeat dose study in NHPs
Quality Assurance

The establishment of Morphic’s Quality Systems is mandated by the ICH Q7 and Q10 guidances that are adopted by most of the regulatory agencies worldwide. These systems, including hardware, software, standard operating procedures (SOPs), under the direction of Morphic Quality Assurance, will cover all regulated activities, including good manufacturing, laboratory and clinical practices (GMP, GLP, and GCP, respectively). Quality Assurance activities will encompass risk assessment across all functions (e.g., product, patient, information technology, nonclinical, clinical, compliance, regulatory, business development and supply chain/chain of custody).

- Quality plan, Risk management
- Implementation of Quality systems supporting GXP activities
- Standard Operating Procedures (SOPs), work policies/instructions
- Corrective and preventative action (CAPA) plans
- Site-specific qualifications and audits (in-life/process when possible) reporting
- Change control (quality planning and control of revisions to specifications, process parameters, procedures) oversight and reporting, as needed
- Trend analysis reports

The work on the Quality Systems commenced in August 2018. Plan to implement first few SOPs early March 2019.
Program and Alliance Management

The significant increase in the complexities of Morphic development programs as they approach IND coupled with the anticipated need to manage the alliance with AbbVie biopharma partner has led us to implement Program Management as a distinct function. Morphic Program Management, which now includes Kris Hahn, intends to keep project activities efficient and external stakeholders aligned while maintaining maximal operational flexibility. To date, we have hosted the Joint Governance Committee kick-off introductions call December 2018 and the official face-to-face kick-off meeting in January 2019. All AbbVie and Morphic JGC members remain enthusiastic about our path forward. Functional heads at Morphic have updated subject matter experts at AbbVie to gain agreement on detailed path forward. Separate JGC minutes are available upon request.

P&M efforts include:

- Create and maintain tasks and timelines (TnT) across all programs, including costs and FTEs;
- Integrate Discovery and Development activities;
- Manage relationships with prospective partners to keep ‘living’ timelines on target and continuously improve learning, communication, efficiency, and effectiveness;
- Accurately forecast budgets for the development activities.
Appendix 1. Deliverables to enable an IND [21CFR312, Common Technical Document (CTD) format, ICH M4]

Regulatory (FDA Regional Specific IND Forms, ICH M4 Guidelines, CTD Module 1)
- FDA Form 1571 (IND application, Section 1.1)
- List of contract research organizations (CROs, attachment to FDA Form 1571)
- FDA Form 1572 (Clinical deliverable)
- Cover letter (Section 1.2)
- Form FDA 3674 (Certification of compliance, clinical trials form, Section 1.1)
- FDA form 3454 & 3455 (Clinical investigator financial certifications & disclosures, Section 1.3.4)
- Contact/Sponsor/Applicant information (Section 1.3.1)
- Letter of Authorization (if applicable, e.g., DMF, Certificate of analysis, Section 1.4.1)
- Environmental Analysis (CMC/Nonclinical deliverable, Section 1.12.14)
- General Investigational Plan (Clinical Synopsis, tabular description of Phase 1 plans, Section 1.13.9)
- Draft Labeling (typically based on TPP, Section 1.14.1)
- Investigator’s Brochure (Section 1.14.4) Nonclinical/Clinical Deliverable, usually only have animal data to characterize patient risks for IND
- PreIND correspondence (Section 1.12.1)

Chemistry, Manufacturing, and Controls (CMC, 21CFR211, ICH Q Guidelines, CTD Module 2 & 3), sufficient information to ensure proper strength (potency, concentration), identity, purity and quality (strength, ID and purity over time in various conditions)
- Quality target product profile (QTPP) and ID of critical quality attributes (CQA), including particle size, polymorphic form, dissolution/disintegration, water content, light protection and impurity control (etc.)
- CGMP [(501(a)(2)(B)] manufacturing process, using flow/schematic diagram(s) plus text descriptions incorporating QTPP and CQA elements with process improvement, control, and robustness (typically QbD not required till Pre-NDA)
- Batch formula/records (precise and detailed description of pharmaceutical manufacturing ingredients and processes) for the material used to support animal studies (namely GLP toxicity studies and clinical trials)
- Quality overall summary (Section 2.3, M2 of CTD), written descriptions of drug substance and drug product, to include comparison text and tables to TOX material used in GLP toxicology studies
- Module 3 (M3 of CTD) Written and tabulated descriptions of drug substance, drug product, appendices for raw data, regional information

CONFIDENTIAL
(country specific) and literature references

- Written descriptions of analytical procedures (Quality Control) and specifications with data qualifying assays, certificate of analysis for bulk drug substance and drug product specifications (to match or exceed testing done on TOX material), demonstrate control of drug substance, excipients and intermediates, process controls, container closure system, description of placebo (if used), labeling and environmental assessment.

Nonclinical [21CFR58, ICH M3(R2) & S Guidelines, CTD Module 2 & 4], description of the pharmacological (beneficial) and toxicological (adverse) effects and the mechanisms of action of the drug in animals and information on the absorption, distribution, metabolism, and excretion of the investigational product, if known

- Nonclinical overview (Section 2.4, Module 2), a brief single paragraph description of the molecule, clinical plan, pharmacology, pharmacokinetics and toxicology studies with a bulleted list or single table listing completed included studies
- Pharmacology (Section 2.6.2 & 3, Module 2), written and tabulated summaries of disease models used to support the ‘intended use’ in normal healthy volunteers and ultimately patients (activity will be led by Discovery Organization)
- Pharmacology reports (Section 4.2.1, Module 4), relevant disease model study reports or Morphic scientist peer-reviewed publications with actual study data (activity will be led by Discovery Organization)
- Pharmacokinetics (Section 2.6.4 & 5, Module 2), written and tabulated summaries of absorption, distribution, metabolism, and excretion of a drug candidate
- Pharmacokinetics (Section 4.2.2, Module 4), any study report specifically done to investigate PK, often these data are generated and reported in toxicity studies
- Toxicology (Section 2.6.6 & 7, Module 4), written and tabulated summaries of adverse effects of drug candidate characterized by in silico, in vitro and in vivo studies
- Toxicology (Section 4.2.3, Module 4), integrated audited draft toxicology reports

Clinical (21CFR50, 56, ICH E Guidelines, mainly E6, CTD Module 2 & 5)

- Clinical overview (Section 2.5, Module 2), few page description of the clinical plan, indication, route, dosing frequency and duration, rationale and justification, including proposed starting dose and dose escalation scheme with relevant literature references
- Patient informed consent form (ICF, Section 5.3.3.2, Module 5)
- Investigator’s brochure (Section 1.14.4, Module 1), typically only have animal data to assign patient risks
- FDA form 1572 (for each Investigator with Curriculum Vitae