Gene Therapy Platform using Certara's Virtual Twin™

Proven, *In-silico* Dose Optimization Technology for Novel Modalities

The Promise of Gene Therapy

By 2025, the US FDA expects to approve 10-25 new gene therapies a year. Gene therapy works by replacing a gene that is missing or dysfunctional, or turning off genes that are causing medical problems. Oftentimes, the defective gene is missing from birth, but it can also mutate later in life. Gene therapy is typically a one-time treatment which would permanently change the medical health of the patient. It does this by reversing or halting the disease, eliminating the underlying cause of that disease.

Key Challenges in Gene Therapy Drug Development

As gene therapy is a new drug modality, successful development requires new types of expertise:

- The inherent manufacturing challenges in gene therapy can slow clinical trials,
- As many gene therapy candidates are for rare disease, patient recruitment can be difficult,
- Working with regulators and gaining approval for novel clinical plans is often a new paradigm,
- Finally, the single-dose delivery of gene therapy cannot be determined using traditional dose determination methods, such as PK/PD.

Getting the Dose Right

In most cases, you have one chance to deliver gene therapy to a patient. Considered personalized medicine, each 'therapy' is based on individual patient data detail to repair or enhance faulty genes. Because each patient is different, the dose and administration of that gene therapy must differ as well. So, if you are too cautious and give too low a dose, a patient may not receive any benefit of the treatment. On the other hand, giving too high a dose can be very dangerous, since any side effects may be irreversible and may last for years if not decades. In short, the definition of a narrow therapeutic index takes on a completely new meaning in gene therapy.

Dose selection for gene therapy is like hitting a bullseye—too little will inhibit efficacy and too much can cause a serious safety issue.

# Certara's Virtual Twin Technology

Certara's Virtual Twin technology creates a computer-simulated model of each patient, replicating the patient's various attributes that affect a drug's fate in their body and hence its effects. Virtual Twin allows drug developers and clinicians to predict the optimal drug dosing regimen for an individual patient – one that maximizes therapeutic benefit while minimizing side effects – by evaluating the impact of different drug doses, schedules, and combinations in the patient's *in silico* 'virtual twin' first. This technology is a component of Certara's industry-leading Simcyp™ physiologically based pharmacokinetic (PBPK) and quantitative systems pharmacology (QSP) platforms, and has determined dosing and other label claims on many approved novel drugs.

Gene Therapy Case Study Using Virtual Twin

A mechanistic model (using QSP) gene therapy platform was developed and further adapted for the rare disease treatment under investigation. Inputs to the platform included patient morphology factors such as age, including pediatrics, gender, weight, height and varying doses. We then predicted organ and plasma volumes from the morphology as well as several uncertainty factors and ran the simulations in the platform. Based on those outcomes, we provided individualized dosing recommendations (from virtual twin) tested in early clinical studies. Each of these dosing predictions were successfully applied to individual patients in the phase 1/2 trial. The model was then used to generate virtual trials to determine the dosing approach for the phase 3 clinical study submitted within the regulatory package.

Real-time, iterative and personalized dosing using Certara's Virtual Twin™ technology for gene therapy is here
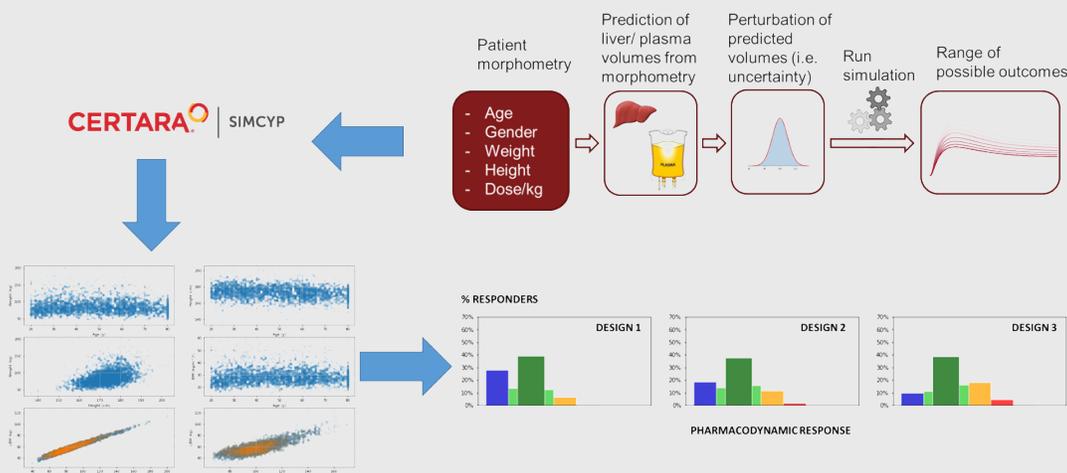
The QSP model enabled us to create virtual twins to individualize the dosing for each patient and simulate virtual trials exploring different dosing regimens and trial designs. This QSP model-informed precision dosing approach was validated with real patients in early clinical trials and used for dose selection in phase 3 trial design.

About Certara

At Certara, we accelerate medicines to patients, partnering with life science innovators. Together we advance modern drug development with biosimulation, regulatory science, and market access solutions.

For more information, visit **www.certara.com**.