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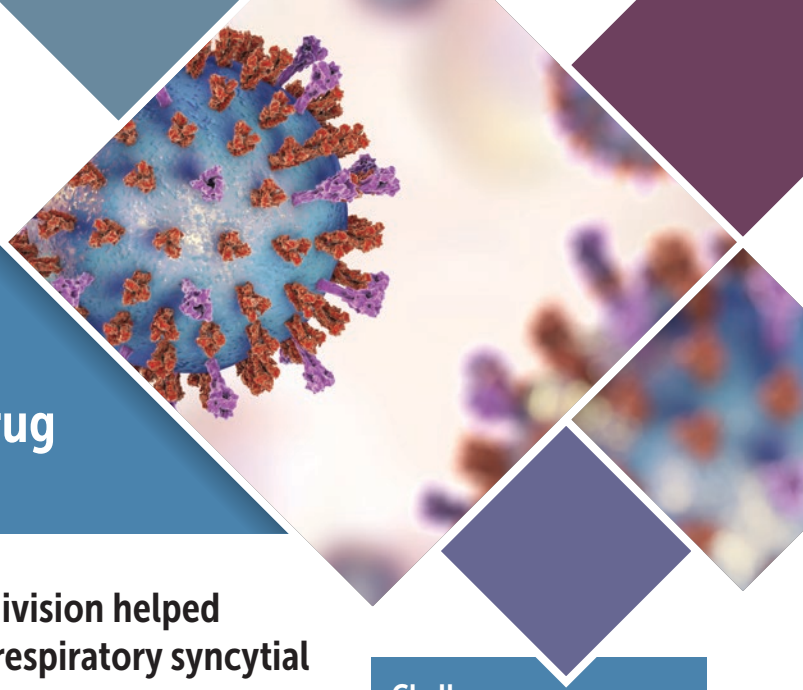

Crafting a Translational Medicine Strategy for a Pediatric Antiviral Drug

Scientists from Certara's Strategic Consulting division helped Alios Biopharma develop a novel drug to treat respiratory syncytial virus (RSV) infection in infants

Background

In pediatrics, traditional development methods can be problematic for ethical and logistical reasons. After all, children are not small adults. They are a heterogeneous population, especially neonates and infants, as organ maturation affects drug exposure and response.

In this case, there was no precedent for regulatory acceptance of an accelerated pathway for a small molecule anti-viral drug to treat RSV (respiratory syncytial virus) infection in infants. RSV primarily affects children who are two years of age and younger. All children will be infected, but a subset will develop significant disease that may result in hospitalization or mortality. RSV has also been associated with the development of recurrent wheezing and asthma in children later in life. Immunocompromised adults and the elderly also can contract RSV infections. No drugs have been approved for treating RSV infection. Thus, the current standard of care is supportive.

Challenge

Alios Biopharma was working on developing ALS-8176 as a treatment for RSV. It is a novel pan-genotypic nucleoside analog inhibitor of viral replication. ALS-8176 is administered orally as a pro-drug. It's activated intercellularly to the triphosphate form which results in inhibition of viral replication via chain termination.

There was no precedent for regulatory acceptance of an accelerated development pathway for an anti-RSV small molecule drug for infants. Determining when and how to conduct pediatric studies knowing that the population of relevance is infants who are less than two years of age was of critical importance.

Solution

Certara's Strategic Consulting, in collaboration with scientists at Alios Biopharma, helped design and shepherd a translational medicine strategy to support the early clinical development of ALS-8176. The approach was to conduct a healthy volunteer single ascending dose/multiple ascending dose

Challenge

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Solution

Certara's Strategic Consulting, in collaboration with scientists at Alios Biopharma, helped design and shepherd a translational medicine strategy to support switching from adults to infants at the end of Phase 2a using pre-clinical models, disease and PK/PD M&S, and clinical pharmacokinetic (PK), viral kinetic (VK) and safety data from healthy adults and adaptive-design human challenge models (HCM).

Benefit

Health authorities accepted the accelerated pathway. The time and cost savings from the adaptive HCM design was estimated to be about six months and $13M.

(SAD/MAD) study. PK data was then collected from a pediatric SAD/MAD study conducted on hospitalized infants with RSV. PK modeling with allometric scaling was used to justify pediatric dosing to achieve concentrations that were expected to be in the therapeutic range based on pre-clinical animal studies.

Specifically, after dosing about 60 healthy volunteers, the next patient who received this drug was an infant.

In parallel to the infant clinical study, an adult healthy volunteer challenge study was conducted to generate exposure-response data to show proof-of-concept and further define the exposure-response relationships.[1] The results of the adult RSV challenge study demonstrated antiviral activity of ALS-8176 and elucidated the exposure-antiviral relationships.[1]

The results of these data sets allowed the construction of a PK/PD and viral kinetic model for RSV in adults.[2] The pharmacokinetic model links plasma concentrations to lung triphosphate drug concentrations.[2] These models enabled determining the exposure-response relationship.

To provide initial estimates of PK parameters and the impact of dose on inhibiting viral replication, standard allometric scaling of clearances in volumes, including incorporating a renal maturation factor, was used. This was utilized to estimate a Phase 1 starting dose in pediatrics that had sufficient safety margins to pre-clinical species and to exposures obtained in adults. This starting dose was also expected to be in the low-therapeutic range because this model initially was purely based on adult data, without any pediatric information. The model was updated and adjusted over the course of the study as data were collected.

Benefit

This is one of the first examples whereby a small molecule drug program has successfully taken this integrated clinical/pre-clinical pharmacology and modeling & simulation approach to go into clinical study in infants very early in development.

Impact

Health authorities accepted this accelerated model-informed development approach. The time and cost savings from the adaptive RSV human challenge model (HCM) design was estimated to be about six months and up to $13M. Based on the strength of the data, Alios was acquired by Johnson & Johnson.[3]

The use of clinical pharmacology tools was essential to supporting the continued development of this new anti-RSV drug which stands to benefit some of our smallest patients.

> "We engaged d3 Medicine [a Certara company] to help us challenge conventional pediatric development paradigms for our RSV program."
>
> – Dr. Sushmita Chanda, VP, Alios Biopharma

References

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2. Patel K, Kirkpatrick C, Nieforth K, Chanda S, Zhang Q, McClure M, Fry J, Symons J, Blatt L, Beigelman L, Smith P. Population PK/PD Modeling of Human Respiratory Syncytial Virus Infection and the Antiviral Effect of AL-8176. Presented at ID Week. October 7-11, 2015, San Diego, CA.

3. Johnson & Johnson Announces Completion Of Alios Biopharma Acquisition. https://www.jnj.com/media-center/press-releases/johnson-johnson-announces-completion-of-alios-biopharma-acquisition (2014)

About Certara

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