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Evaluating the Competitive Landscape to Support a Best-in-class Strategy

Certara Strategic Consulting scientists used model-based meta-analysis (MBMA) to support dose optimization and product positioning of a psoriasis drug.

Background

Psoriasis is an auto-immune disease characterized by abnormal patches of skin. The sponsor needed to select the dose-range for Phase 2 studies of a novel drug for psoriasis using Phase 1b data. The Phase 1b data showed a strong proof-of-concept for drug efficacy; all active treatments resulted in a maximal therapeutic effect by the end of the study.

Challenge

Due to limited Phase 1b data from a small number of patients, no robust pharmacokinetic/pharmacodynamic (PK/PD) model could be established. While the sponsor determined an initially proposed dose (25-200 mg, injected subcutaneously at specified time points) range, they were concerned whether this range would permit characterizing the dose-response relationship for the drug and determining the lowest maximum effective dose.

Solution

To borrow strength from published comparator data, MBMA was proposed for conducting a comparator analysis to enable model-based dose selection for Phase 2 studies.[1,2] This best-in-class strategy would support maximal learning in Phase 2 to help the sponsor understand the requirements for Phase 3 dosing.

The comparator analysis drew upon mean study-arm level data from five commonly used psoriasis drugs—adalimumab, etanercept, infliximab, ustekinumab, and briakunumab (Figure 1). The combined data set included information on over 10,000 patients.

Before starting the comparator analysis, four critical assumptions were made. First, the maximum efficacy for the in-house compound was assumed to be similar to other compounds with similar mechanism-of-action (MOA). Next, the time-course of the onset of response was presumed to be

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Benefit

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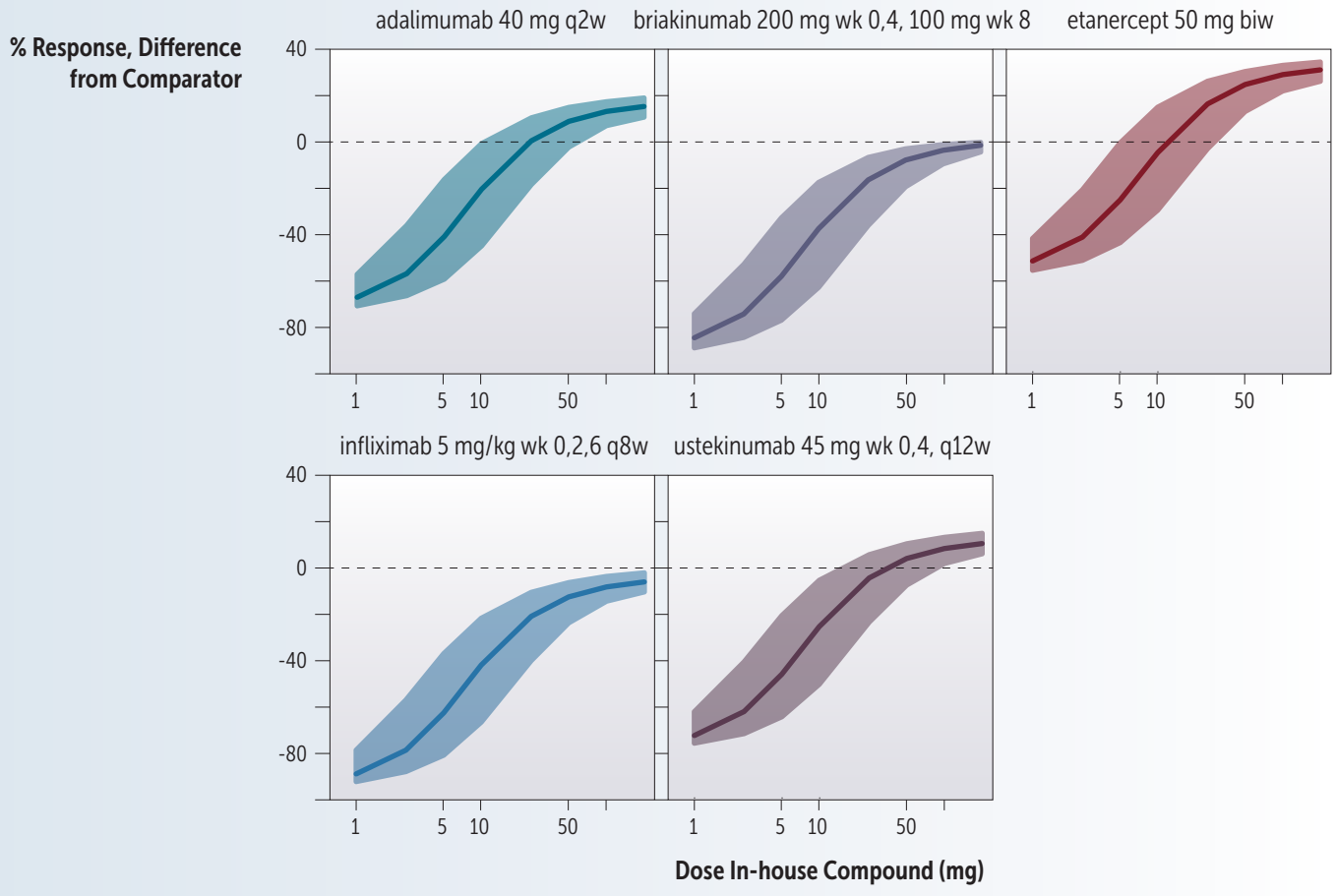
similar across compounds. In addition, the efficacy of the Phase 1b dose regimen of the in-house compound was expected to be similar to the efficacy of the Phase 2 dose regimen. Finally, the Phase 1b and Phase 2 patient populations were assumed to be similar.

Figure 1. The comparator analysis combined mean study-arm level data from over 10,000 psoriasis patients

Compound		MoA	# Trials	# Study arms incl. plac	# Patients
Adalimumab	(Humira)	Type 1	4	9	1658
Etanercept	(Enbrel)	Type 1	9	20	2868
Infliximab	(Remicade)	Type 1	6	15	1695
Ustekinumab	(Stelara)	Type 2	5	13	2868
Briakinumab	(ABT-874)	Type2	2	6	1585
In-house compound			1	5	24

Comparative efficacy models were used to determine the time-course of the response for the drugs. The models assumed that the maximum efficacy for the in-house compound was similar to competitors with the same MOA. They also assumed that the time-course for the response onset was similar across compounds. These models showed a drug effect that gradually increases over time to a steady-state.

Figure 2. Positioning the in-house compound in the competitive landscape



The in-house compound was then compared to competitors in dose-response models. All compounds were estimated to have different potencies. Limited Phase 1 data meant that there was a large uncertainty in determining the dose-response relationship for the in-house compound.

Clinical trial simulations were then used to optimize dosing for Phase 2 studies. Establishing the dose-response for a drug requires using doses between placebo and maximal effect or plateau. The doses for Phase 2 were evaluated for being "near placebo," "near maximum effect," or in between. The clinical simulations included doses near the ED_{50} in the Phase 2 trial to identify the lowest dose reaching maximum effect.

Benefit

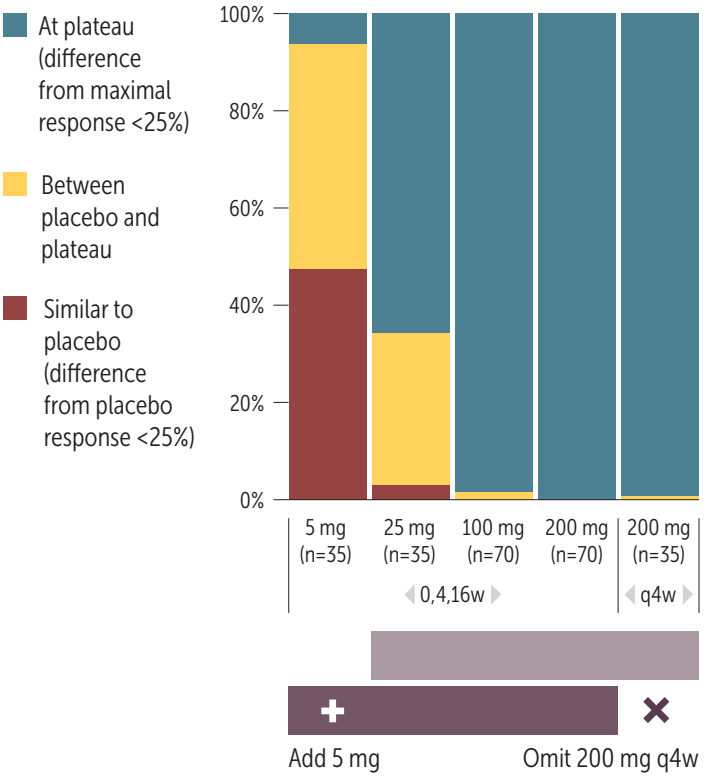
Dose-response models provided several insights regarding which doses to use in future trials. The 50 mg dose was predicted to have a near maximum effect. Doses of 50-200 mg were predicted to have little separation in time to reach maximum effect. Therefore, the 200 mg dose is not predicted to have a faster maximum effect. Also, by determining the median effective dose (ED_{50}) to be approximately 8.4 mg meant that the 5 mg and 25 mg doses would be the best for further establishing the dose-response relationship.

The models also supported positioning the in-house compound in the competitive landscape. Doses greater than 50 mg were predicted to be superior to etanercept, adalimumab, and ustekinumab. However, the similar potency and onset of action conferred no major competitive advantage over ustekinumab (Figure 2).

The clinical trial simulations revealed that the 100 mg and 200 mg doses given on the typical schedule were predicted to be at the plateau of the dose-response relationship (Figure 3).

The monthly 200 mg dose arm was not predicted to be informative, so it was dropped. Because there was a reasonable probability that the 5 mg dose was not near plateau or placebo, this dose was added.

Figure 3. MBMA supports dose selection for Phase 2B study



Impact

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References

1. Kerbusch T. Phase 2b dose selection, leveraging comparator data through multidisciplinary modeling & simulation. *EMA-EFPIA Modelling and Simulation Workshop* (2011).

2. Kerbusch T, et al. Phase 2b dose selection for the treatment of autoimmune disorders leveraging comparator data. *PAGE Meeting* (2011).

About Certara

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