ClinBAY
Statistical solutions to drug development

Evaluating the potential of drug combinations

ClinBAY Solution Series

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Introduction

Many diseases have several drugs approved for their treatment. While each drug on its own has demonstrated a sufficient level of efficacy to reach the market, rarely is research made on the efficacy or safety of combination therapies. Is it a good or a bad idea to combine multiple drugs together? Will combinations work better than either drug on its own? What is the most effective drug combination for a disease or condition? These are important, but rarely researched issues.

Our client is fighting an infectious disease that affects millions of people, leading each year to hundreds of thousands deaths. Several stand-alone treatments are approved and our client is willing to combine them together, for a better efficacy, tolerability and reduced risks of recurrence or resistance.

Each drug has a level of efficacy that increases with dose. The maximum selected dose is such that the product remains safe. There is an expectation from our client that the combination therapies efficacy will be greater than when the 2 drugs are given alone. Doses could hopefully be reduced as much as possible in the combo, to avoid appearance of safety issues while maintaining high efficacy.

Practically, it is not possible to test all treatment combinations at various dose levels in an experiment. Cost would be too high and research too long to conduct, if a combination therapy needs to be compared to each drug alone at various dose levels.

ClinBAY was called to address this problem: How could we determine optimal combination regimen at the lowest possible experimental cost, whilst at the same time limiting risk for the subjects? Our first challenge was to establish a quantitative method that evaluates if a combination is effective. The second challenge was to propose an optimized experimental design for that evaluation. That involved the determination of how many combinations must be run, how many subjects, and at which dose levels.

Methodology

The complexity of the problem has to be acknowledged. The methodology developed below is a product of multiple hours of discussions, literature review and simulations. We believe that the solution selected is practical and has proved its value in multiple cases

First we defined the criterion for success: the combination will be declared to have a positive benefit if its efficacy is superior to the efficacy of each drug given alone. Efficacy of the combo must therefore be superior to the maximum of the efficacy rates for the 2 drugs alone. We decided to quantify the probability of such a positive effect using Bayesian techniques. That Bayesian posterior probability has a direct and intuitive interpretation. It quantifies the level of confidence in moving the combination forward. If probability is large (let say above 80%), chances are large enough that we have a success. If it is low (<20%), there is no confidence and we report a failure.

Second, as efficacy varies with dose, some dose-finding experiments have to be run. The simplest option of running independent factorial designs at each dose level separately was discarded as it was too costly. In that setting, comparisons are made at each dose level combination separately, leading to multiple independent probability tests. However, no information is shared between dose levels and experiments must be repeated each time a new dose combination is considered. Furthermore, multiple testing produces an inflation of the type I error. Finally, when an new combination is evaluated, historical data from the stand-alone drug may not be re-used if different doses are considered.

To avoid these issues, we chose to model the dose-efficacy relationship separately for each stand-alone drug. A parametric model was adjusted to the initial data available for each stand-alone. The model was then updated each time a new scenario of dose level was tested for a stand-alone compound. Additional dose levels could be tested in an adaptive design approach.

To evaluate the efficacy of the combo, the study was split into 2 parts. Part 1 was a pilot

study involving a limited number of subjects. A few dose levels of the combo are tested in Part 1, in a low/low, low/high, high/low, high/high factorial design. The efficacy of the combo is then analyzed using a statistical model having two additive components. The first term is the maximum of efficacy from the 2 models of the stand-alone treatments. The second term is an interaction model, that depends on the dose levels for the 2 drugs. If the interaction is negative or null, there is no added benefit for the combination, as its efficacy does not exceed the maximum efficacy of the stand-alone drugs. If interaction is positive, the combination has some added benefit. Estimation is made jointly for all parameters using Bayesian methods. Probability of a positive effect is calculated across the entire dose-range for the 2 drugs. This permits a global assessment of the combination potential, as well as the identification of a reduced dose-range where to pursue further experiments.

Part 2 is therefore decided adaptively, based on Part 1 results. It may involve more dose levels for drugs alone, if stand-alone models need refinement. For the combo, if Part 1 results are not clear-cut, it will generally focus on the dose range where results were not conclusive (i.e., having only a 50% probability of a positive effect), excluding places where the effect of the combo is either outstanding or poor. Part 2 data are then analysed at the end, in the same way as after Part 1.

Key Findings

This project demonstrated the value of Bayesian methods, visual data presentation and adaptive design of experiments in an important but complex medical problem.

Bayesian methods

Bayesian modelling techniques permit to assess quickly the potential of drug combinations at a limited cost.

Probability of success

Visual display of key results in the form of probability maps enables accurate decisions with confidence.

Adaptive design

An iterative experimental procedure triggers information enrichment over time.

Visual Data

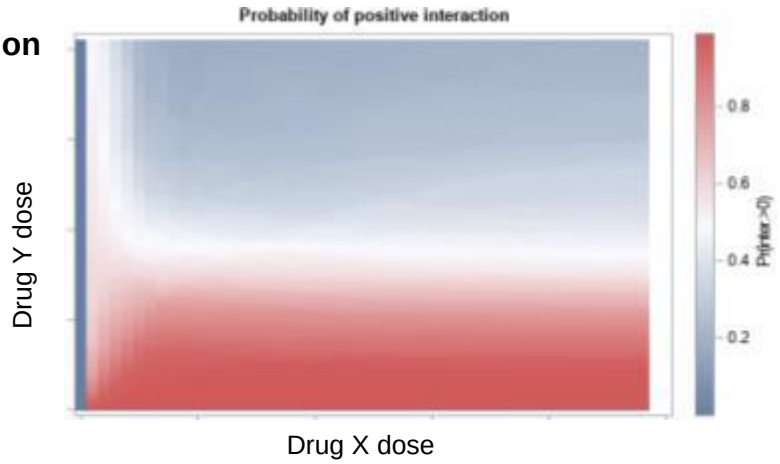
We illustrate the value of the methodology in a case study example.

Dose versus efficacy for 2 drugs alone

Stand-alone dose-response models are adjusted to each drug when administered separately. An adaptive design method is used to identify the need for additional doses response information during Part 2.

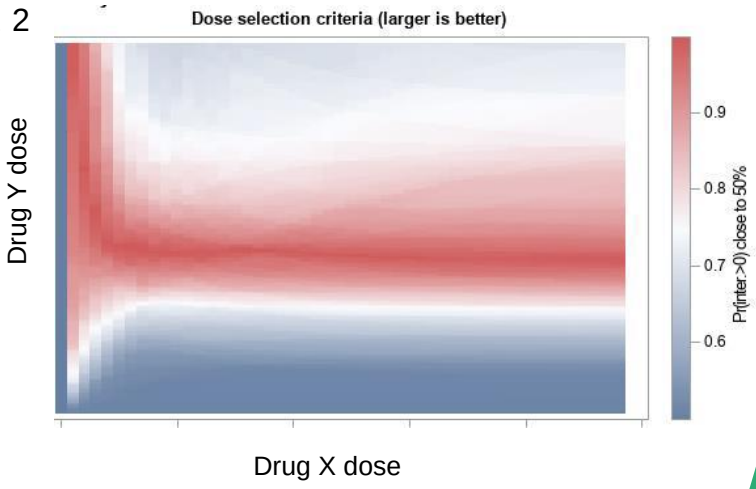
Probability map of a positive combination

A low dose of drug Y combined with any dose of drug X has high changes of a greater efficacy (red zone). When increasing dose of drug Y, value of the combination decreases (blue zone).



Dosing area for Part 2

Red zone is the area where doses for Part 2 should be selected. It represents the inconclusive area at the end of Part 1.



Conclusion

The statistical solution provided to our client, permits a quick and cost-effective evaluation of combination therapies in a life-threatening infection disease. The method has been used successfully at least 10 times at of the time of writing. It produces decision-enabling information, whilst at the same time being reliable and cost-effective.

Key Takeaways

1. Look around for experts who may help you when facing a difficult clinical trial problem.
2. Solutions using information sharing, when implemented correctly, can provide better decisions at lower costs.
3. Small scientific/technology investments can be a good return on investment on the long run.

ClinBAY is a company that provides biometrics solutions to decision makers. Feel free to contact us (info@clinbay.com) if you are interested in our services or products.