Oncology Biostatistics

Bayesian Non-inferiority designs borrowing strength from historical controls with a meta-analytic-predictive approach

Yingbo Wang, Heinz Schmidli, Arunava Chakravartty
May, 2019

Bayes 2019

NOVARTIS

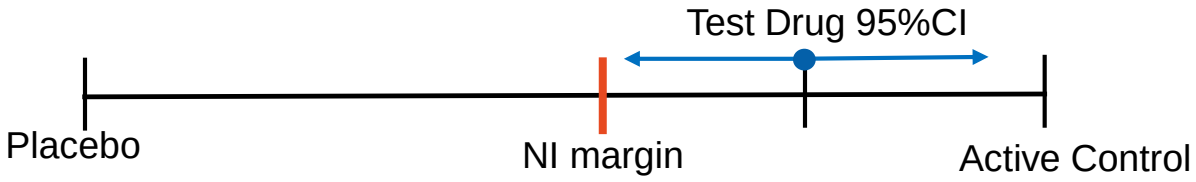
Outline

- Overview
  - Non-Inferiority studies
  - Leveraging historical data
- Case study
- Frequentist design
- Two Bayesian alternatives
- Summary

NOVARTIS

Non-Inferiority studies

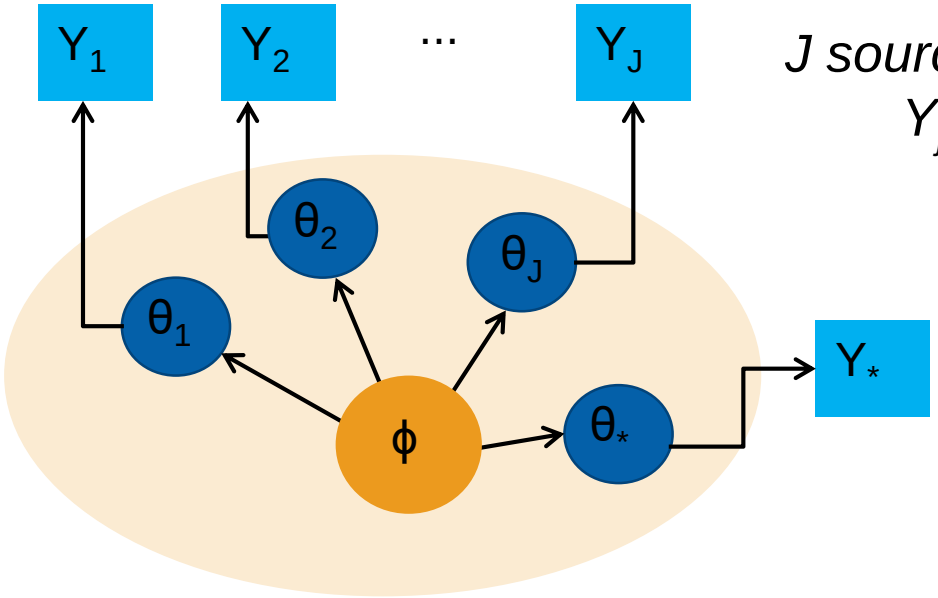
- In a NI study, the objective is to demonstrate the investigational drug has an effect that is sufficiently close to the treatment effect of an active control.
  - NI is established when the lower bound of the 95% CI of the treatment effect is above the NI margin. NI margin chosen a percentage (~50- 75%) of the active treatment effect.



- In many indications , a concurrent placebo control may not be feasible , requiring NI to be established directly with respect to the active control.
  - NI margin based on active treatment effect of historical trials containing placebo control.
- There may be additional opportunities to leverage the historical data beyond the NI margins.
- FDA Guidance for industry – Non-inferiority clinical trial to establish effectiveness https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf
  - **Bayesian methods** that incorporate historical information from past active control studies through the use of prior distributions of model parameters provide an alternative approach to evaluating non-inferiority in the NI trial itself.
- EMA Guideline on the choice of non-inferiority Margin – https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf

NOVARTIS

Considering a Bayesian approach for NI design to leverage historical data



J sources of historical data

$Y_j \mid \theta_j \sim F_j(\theta_j)$

$p(Y_j \mid \theta_j)$

New source of data (plan)

$Y_* \mid \theta_* \sim F_*(\theta_*)$

$p(Y_* \mid \theta_*)$

Hierarchical model to link parameters (hyper-parameters ϕ)

$(\theta_*, \theta_1, \ldots, \theta_J) \mid \phi \sim G(\phi)$

$p(\theta_*, \theta_1, \ldots, \theta_J \mid \phi)$

- Bayesian inference on unknowns $Y_*, \theta_*, \theta_1, \ldots, \theta_J, \phi$
- **At the design stage, MAP (Meta-Analytic-Predictive) prior is derived for θ_* based on historical data $Y_1, Y_2, \ldots, Y_J$**
- Novartis implemented MAP with **R-package (RBesT)** - **B**ayesian **E**vidence **S**ynthesis **T**ools

NOVARTIS

Case Study

- Drug A is approved in a cancer indication at a certain dose as an add-on therapy
- The interest is to explore if a **lower dose** of Drug A could provide a better safety profile **while maintaining similar efficacy (in term of ORR after 6 months)** as the approved dose within **mandated timelines**.
  - Since the Drug A has demonstrated substantial efficacy gain in comparison to the placebo, it will NOT be ethical to add a placebo arm.
- Therefore, the reduced dose of Drug A has to be compared to the approved dose (active control)
- Specifically, it is required to demonstrate that the **reduced dose** of Drug A is **not inferior to** the approved dose in treating cancer patients
  - Active Treatment effect for the NI margin is based on the historical Phase III study

NOVARTIS

Non-inferiority Margin Calculation

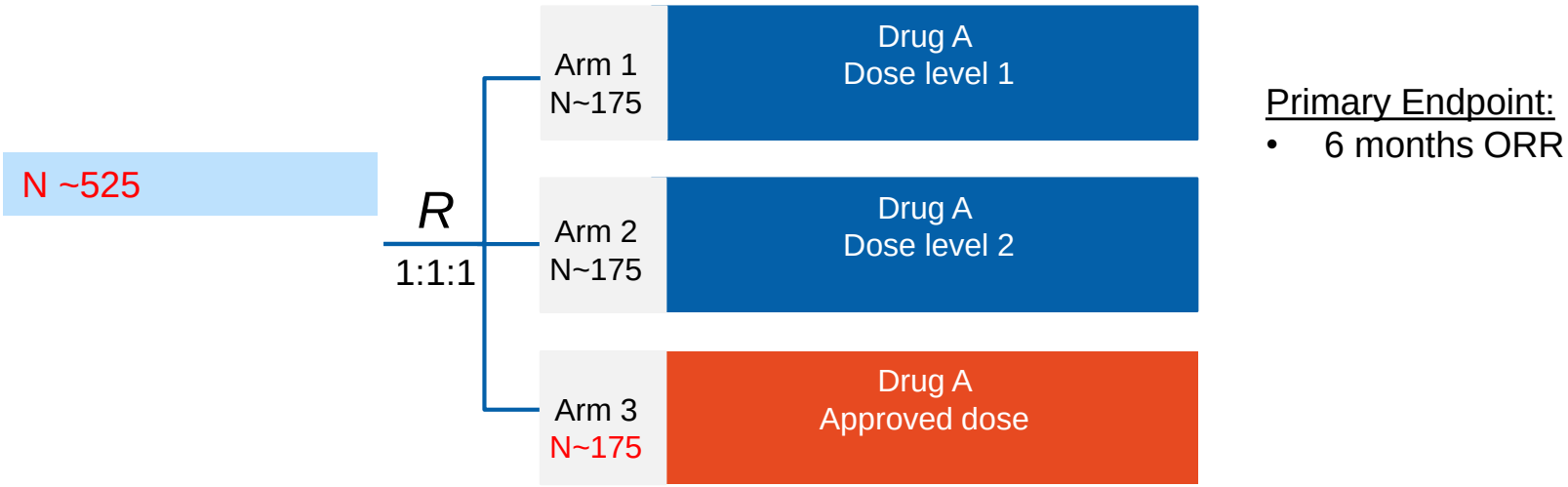
- It was proposed to have **50% of the active treatment effect** of drug A retained in this study in terms of ORR improvement

	Hist. Drug A	Hist. PBO
Total patients with measurable dis.	**257**	**245**
Responders within 6 months	**115**	**73**
6 month ORR	**44.7%**	**29.7%**

- The ORR improvement from historical trial expressing as a ratio:
  - 29.7%/44.7% = 0.664
- Exp(Log (0.664) *(1-0.5)) = 0.815 (**NI Margin**)
- Which means the NI threshold for the lower 90% CI >**36.4%** (i,e, 0.815*44.7%) if the ORR of control arm of the new study is the same as the historical studies 44.7% (with absolute difference 8.3%)

NOVARTIS

A 3-arm NI Design



Primary Endpoint:

- 6 months ORR

- Primary Analysis for each Arm i=1,2 vs Arm 3 (active control) to be based on statistical hypothesis for ORR ratio:

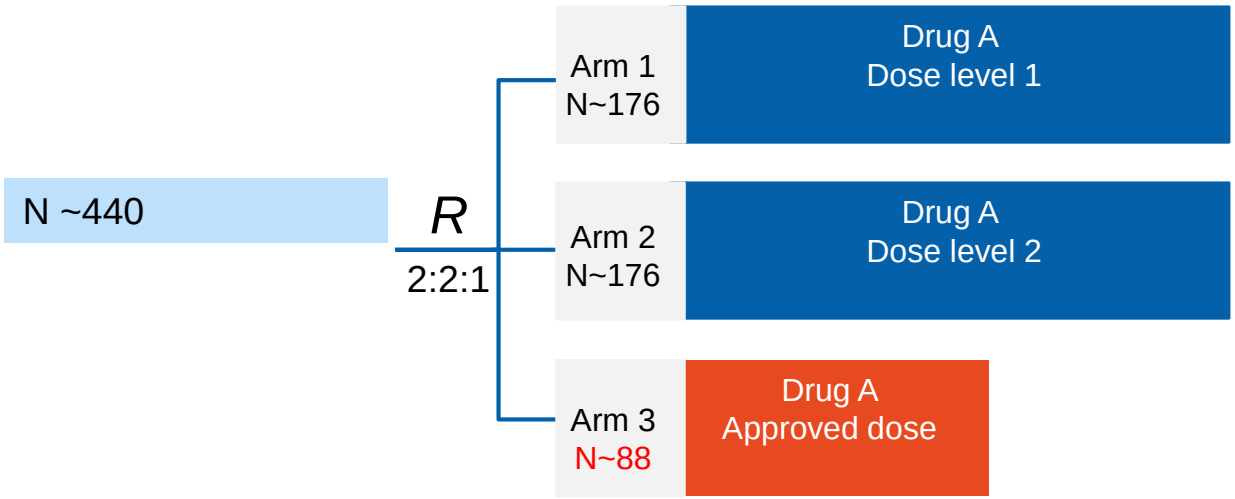
  $$\boldsymbol{H_0: \theta \leq 0.815 \text{ vs } H_1: \theta > 0.815}$$

  $where\, \theta = \frac{ORR_i}{ORR_{Arm\,3}}$ with the goal to demonstrate its 90% lower CI>0.815 for H1
- ORR is overall response rate, which is the percentage of complete response and partial response with all patients randomized in each arm as denominators,
- Sample size ~ **175** patients per arm will provide 80% power for the lower 90% CI to cross NI margin when true ORR ratio is 1.1
- However, the total sample size of **525** appears to be high and the historical information has not been taken into account

NOVARTIS

Bayesian 3-Arm design

A Bayesian design allowing to borrow information from hist. trial



Primary Endpoint:

- 6 months ORR

- Primary Analysis for each Arm i=1,2 vs Arm 3 (active control) to be based on the posterior distribution of ORR ratio:

$$\boldsymbol{Posterior\ Prob}\left(\frac{\boldsymbol{ORR_i}}{\boldsymbol{ORR_{Arm\ 3}}} > \boldsymbol{0.815}\right) > \boldsymbol{95\%}$$

- Fewer patients needed on active control arm due to borrowing from historical data

NOVARTIS

Meta-analytic-predictive approach

MAP Prior for Active Control ORR

- J historical studies with binomially distributed endpoint
- Number of responders in control group from j-th study

  $r_j \mid \pi_j \sim \text{Binomial}(\pi_j, n_j)$

  with number of control patients n_j , j=1,…,J
- Control proportion in new study π_*

Hierarchical model for transformed parameters $\theta_j = \text{logit}(\pi_j)$

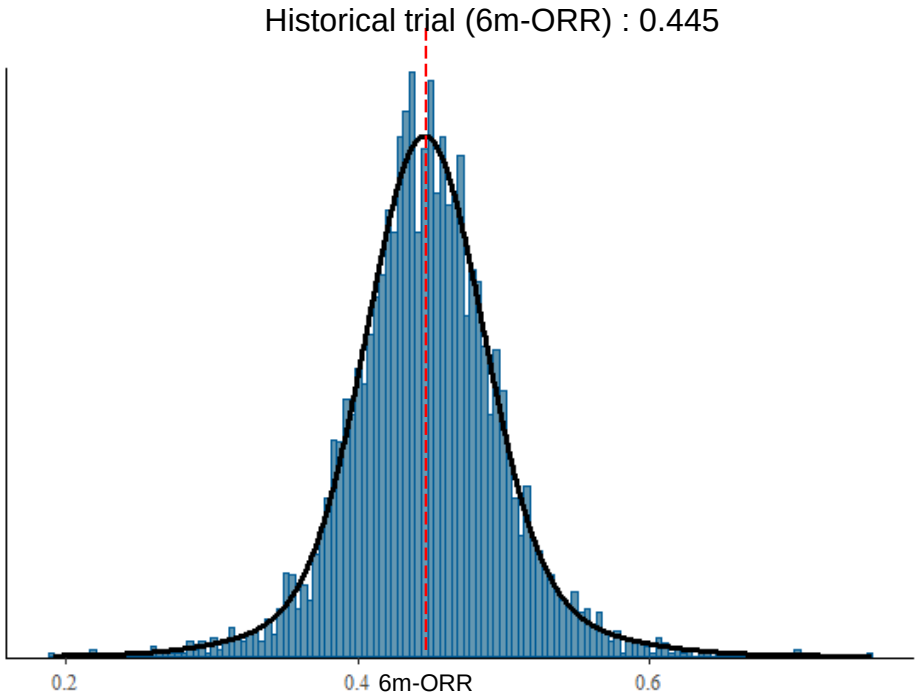
$$\theta_*, \theta_1, ..., \theta_J \mid \mu, \tau \sim \text{Normal}(\mu, \tau^2)$$

Mean μ , between-trial standard deviation τ

MAP for binary data: Neuenschwander et al. (2010), Schmidli et al. (2014)

Prior Specification

- A **non-informative prior** is proposed for Arms 1 and 2 - Beta(1,1)
  - Due to no prior data on the alternative starting doses
- A meta-analytic prior (MAP) is proposed for the Arm 3 (standard dose).
  - Historical 6m-ORR data: 115 (44.5%) responders out of 257 patients.
  - In order to account for a moderate between-trial heterogeneity a Half-Normal $(0, s)$ prior used to **discount for inter-trial variability**
  - s is set to 0.125 times the sd of response to reflect a moderate heterogeneity reflecting **similar population**
  - Using a MAP approach the prior approximated as a mixture of 2 Beta's



$$0.789 \cdot Beta(72.5, 89.8) + 0.211 \cdot Beta(15.8, 19.13)$$

NOVARTIS

Combining study data with historical data

Fully Bayesian borrowing from hist. data via MAP prior

- Declare NI if

$$Posterior\ Prob\left(\frac{ORR_i}{ORR_{Arm\ 3}} > 0.815\right) > 0.95$$

- Posterior calculations via log-link transformation.
  - MAP prior used for $ORR_{Arm\ 3}$ based on historical data 44.7% (38.6%, 51.1%)
  - Sample Size chosen as : 88 patients (Arm 3), 176 patients (Arm 1 & 2)

Powers under different scenarios true ORR in Arm 3

ORR-i/ ORR-Arm 3	38%	40%	42%	44.7%	50%
1.1	48.8	62.4	74.4	86.2	96.1

- Frequentist NI design(no borrowing) : 175 patients in each arm

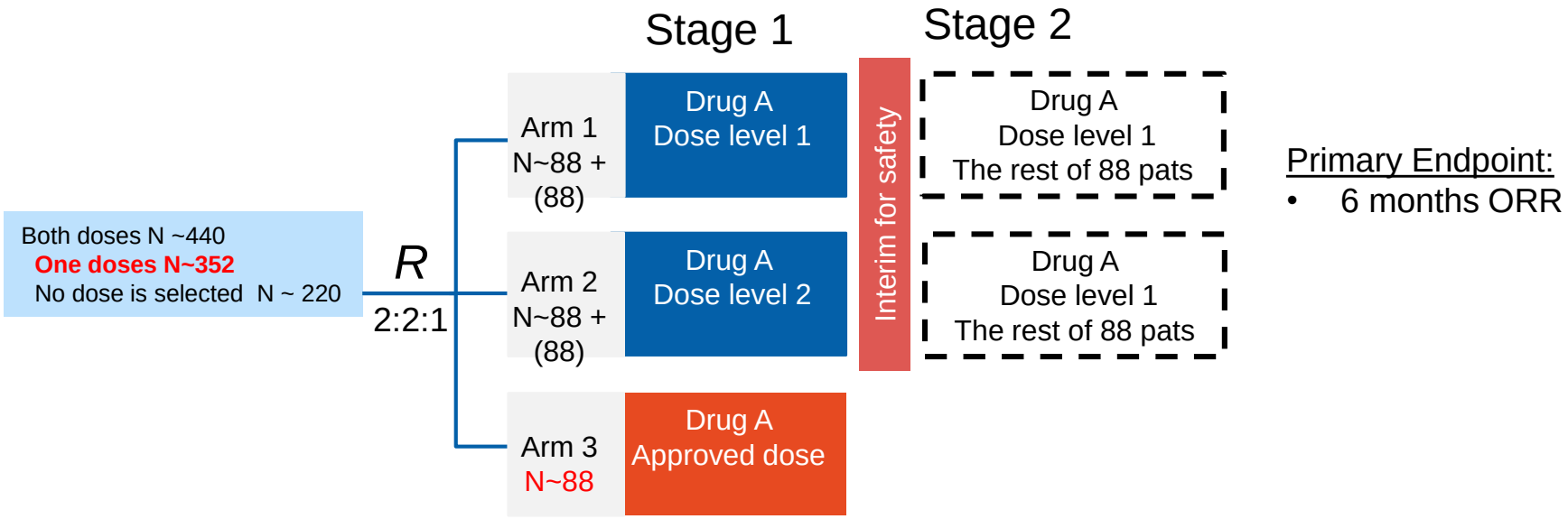
ORR-i/ ORR-Arm 3	38%	40%	42%	44.7%	50%
1.1	70.5	73	75.5	80	87.3

- Due to borrowing from hist. data , Bayesian method has higher power than Freq when true ORR is close to the historical data
  - As True ORR gets smaller than the historical ORR , the power of Bayesian design drops more rapidly than frequentist.

NOVARTIS

Bayesian 3-Arm two stage extension

A Bayesian design allowing to borrow information from hist. trial



- Primary Analysis for each **Inv arm vs control** to be based on

$$\boldsymbol{Posterior\ Prob}\left(\frac{\boldsymbol{ORR_i}}{\boldsymbol{ORR_{Arm\ 3}}} > \mathbf{0.815}\right) > \mathbf{95\%}$$

- Interim analysis for safety assessment is placed after half of the patients enrolled for Arm 1 and Arm 2.
- Safety assessment is based on **the upper 90% CI of QT interval that needs to be <20ms**
- The remaining patient will be enrolled for the arm only if the pre-specified safety criteria is satisfied for that arm.
- In the case that only one dose level is carried forward, the sample size will be **352**

NOVARTIS

Operating Characteristics [1/2]

Null Scenarios in either QT or Efficacy

- True ΔQT_{dose1}=20; ΔQT_{dose2}=20 (**Safety Null**)
- Efficacy in both arms set at 1.1, i.e. $\frac{ORR_i}{ORR_{Arm\ 3}}$=1.1

	Selection Prob at interim (%)	Final Safety Success (%) #	Final NI Success (%) #
Overall		4	8.3
Dose 1	5	37.9	81
Dose 2	5.2	39.8	82.8
Futile(Due to QT)	89.8		

Marginal probability for Overall, Conditional Probability for Dose 1 and 2

- True ΔQT_{dose1}=14; ΔQT_{dose2}=14;
- Efficacy in both arms set at 0.815 (**Efficacy Null**), i.e. $\frac{ORR_i}{ORR_{Arm\ 3}}$=0.815

	Selection Prob at interim (%)*	Final Safety Success (%) #	Final NI Success (%) #
Overall		98.4	5.1
Dose 1	88.4	99.0	5.2
Dose 2	10.2	99.8	5.1
Futile(Due to QT)	1.4		

*One dose is selected
Marginal probability for Overall, Conditional Probability for Dose 1 and 2

NOVARTIS

Operating Characteristics [2/2]

Different ΔQT Dose response scenarios explored

- True ΔQT_{dose1}=**18**; ΔQT_{dose2}=**16**;
- Efficacy in both arms set at 1.1

	Selection Prob at interim (%)	Final Safety Success (%) #	Final NI Success (%) #
Overall		61.8	56.3
Dose 1	24.3	76.8	80
Dose 2	44.7	96.3	82.2
Futile(QT)	30.9		

Marginal probability for Overall, Conditional Probability for Dose 1 and 2

- True ΔQT_{dose1}=**18**; ΔQT_{dose2}=**18**;
- Efficacy in both arms set at 1.1

	Selection Prob at interim (%)	Final Safety Success (%) #	Final NI Success (%) #
Overall		33.3	34.9
Dose 1	24.8	76.8	80
Dose 2	18.4	79.3	87.3
Futile(QT)	57.3		

Marginal probability for Overall, Conditional Probability for Dose 1 and 2

NOVARTIS

Summary

- A Bayesian decision rule to assess NI can be an useful alternative to a frequentist method.
- Using a meta-analytic-predictive approach may allow a more efficient study design via incorporating the historical data in a similar patient population.
- Especially when the true ORR is close to the one observed in the historical trial, the Bayesian trial with reduced control group could offer even higher power than the classical design with full sample size
- While Bayesian NI design appears to be flexible and efficient for decision making, early consultation and discussion with HA is recommended to gain alignment on the key design aspect.
- The HA review length associated with design complexity also needs to be accounted in a trial with mandated timeline.

NOVARTIS

References

- Gsteiger S, Neuenschwander B, Mercier F, Schmidli H (2013) Using historical control information for the design and analysis of clinical trials with overdispersed count data. *Statistics in Medicine* 32(21):3609-3622
- Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ (2010) Summarizing historical information on controls in clinical trials. *Clinical Trials* 7(1):5-18.
- Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B (2014) Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics* 70(4):1023-1032.
- Schmidli H, Neuenschwander B, Friede T (2016) Meta-analytic-predictive use of historical variance data for the design and analysis of clinical trials. *Computational Statistics and Data Analysis*.
- Weber S, Neuenschwander B, Schmidli H, Magnusson B, Li Y, Roychoudhury S (2019) R package RBesT https://cran.r-project.org/web/packages/RBesT/index.html
- FDA (2016) FDA Guidance for industry – Non-inferiority clinical trial to establish effectiveness https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf
- EMA (2005) EMA Guideline on the choice of non-inferiority Margin – https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf

NOVARTIS

Acknowledgement

Beat Neuenschwander
Pabak Mukhopadhyay
Alaknanda Joshi
Emmanuel Zuber

NOVARTIS