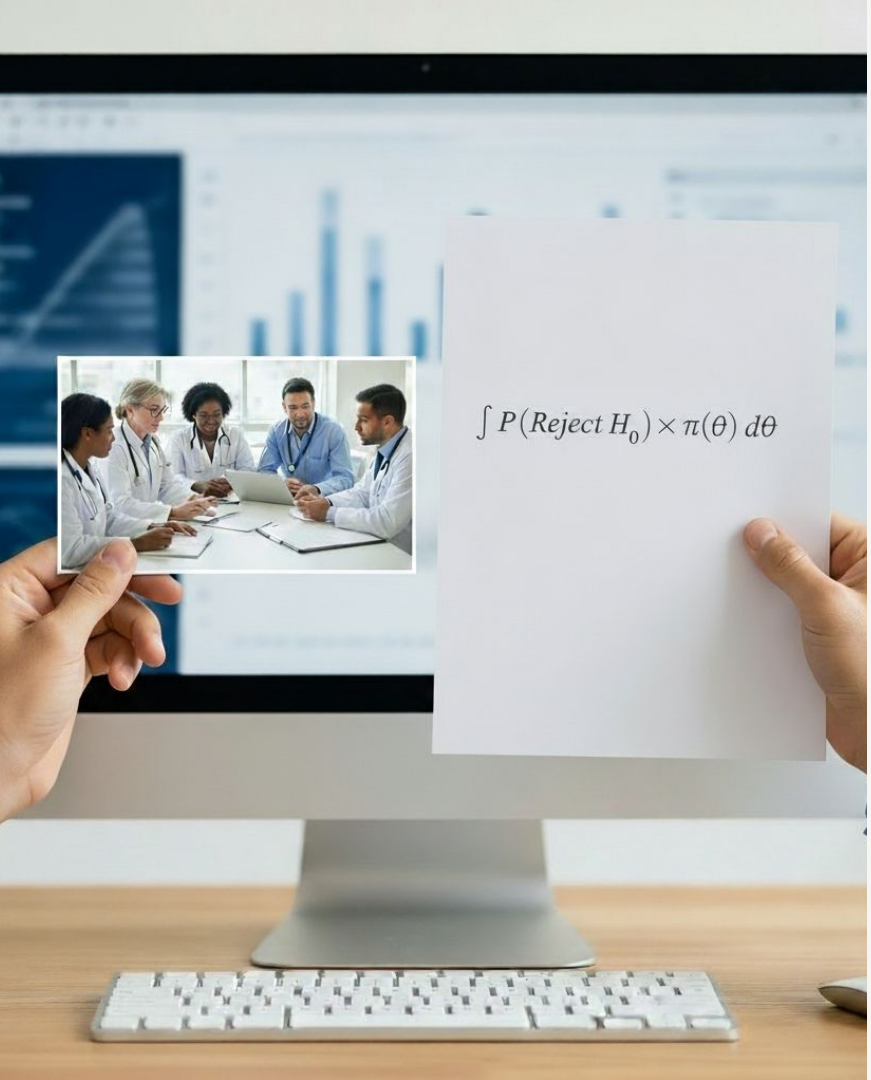

Providentia tries statistics

Harmonizing decision making at Roche

Statistics CoP Forum
October 9, 2025

Godwin Yung, PhD
Statistical Methods, Collaboration, and Outreach Group (MCO)

Thank you

Providentia

Marisa Bottarelli
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Biostats

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Jue Wang
Mark Yan
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Markus Niggli
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Portfolio

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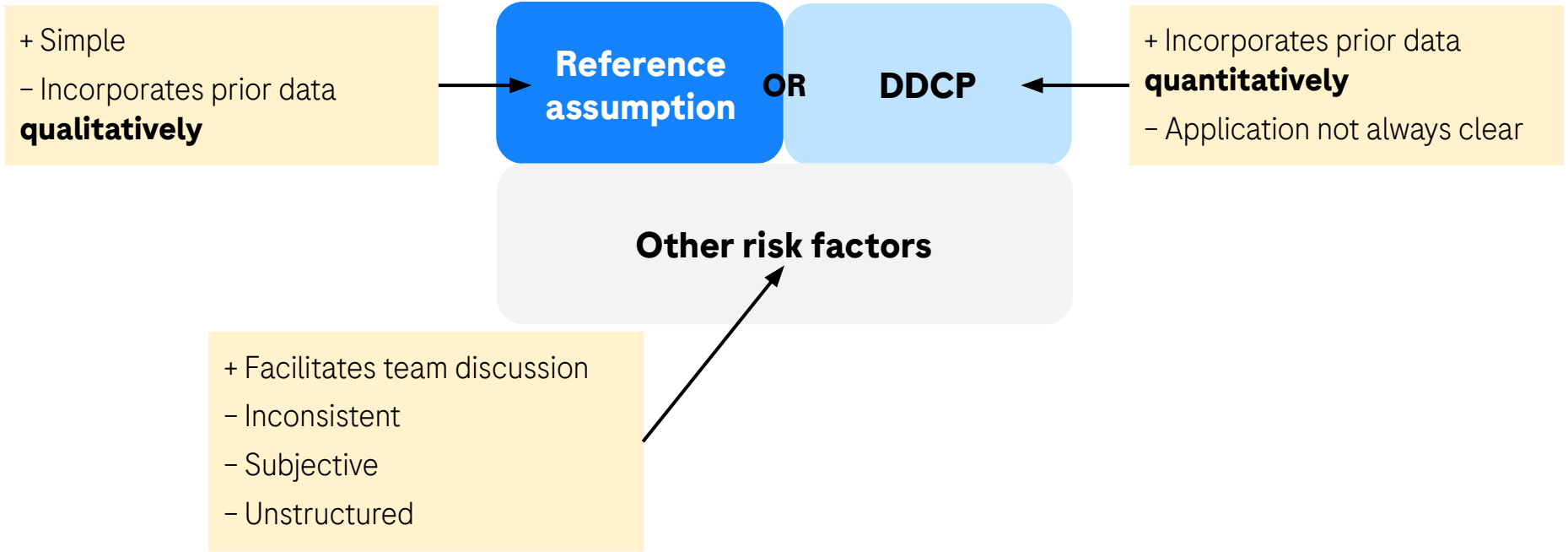
Audrey Baruvka
Alex Ocampo
Alun Bedding
Kaspar Rufibach

Why are we here?

Roche Ph3 cPTS process - 2017

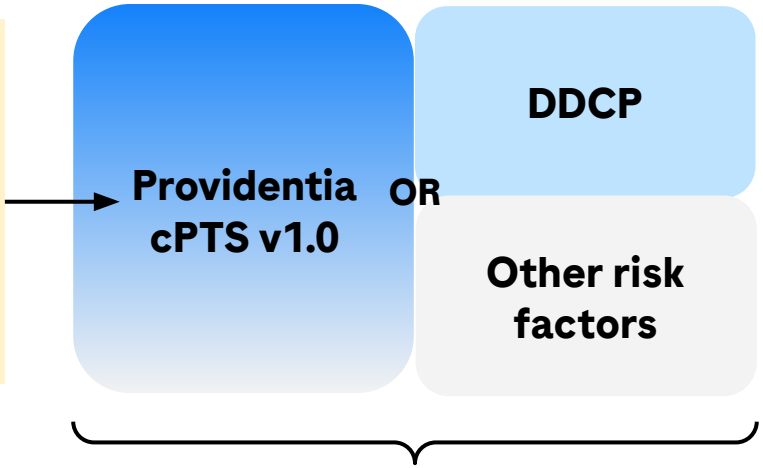
Late Stage PTS Handbook



Roche Ph3 cPTS process - 2020

Providentia is introduced to increase consistency, objectivity, and transparency

+ Consistent
+ Structured
+ Transparent
– Incorporates prior data qualitatively
– “Gaming the system”

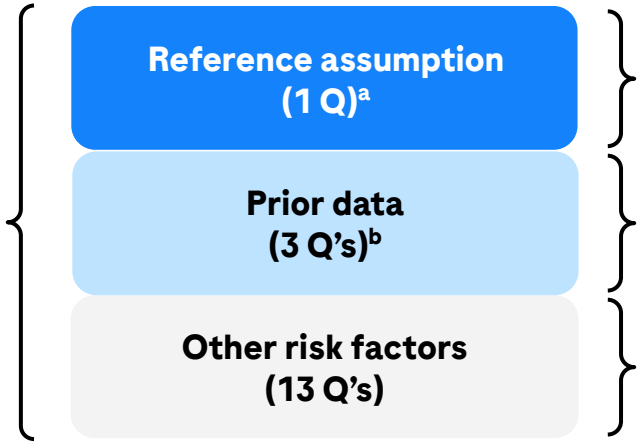


– Inconsistent
– Confusing

Roche Ph3 cPTS process - Q1 2026

Providentia will be updated to harmonize calculation of Ph3 cPTS

+ **Consistent, structured, and transparent** evaluations (Providentia v1.0)



+ Clear **starting point**

+ Impact of prior data *inherits logical behaviors* of **DDCP**

+ Clear relationship between DDCP and **cPTS**

[a] Corresponds to risk factor "Development approach"

[b] Corresponds to risk factor "Strength of treatment effect", which is further broken down into 3 subcategory risk factors, each with their own question: "Magnitude of treatment effect", "Sample size of prior evidence", and "Source of prior evidence"

Providentia cPTS v2.0

- **Clear contribution** of reference assumption, prior data, and other risk factors.
  - **Clear relationship** between reference assumption, DDCP, and final cPTS.

- **Unified** yet **flexible** framework:
  - DDCP is not required to calculate Providentia cPTS.
  - However, if DDCP is available, then it can (A) inform selection of Providentia risk factors, or (B) be directly combined with other risk factors to calculate a Ph3 cPTS.

Providentia cPTS v2.0

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  - **Clear relationship** between reference assumption, DDCP, and final cPTS.

- **Unified** yet **flexible** framework:
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- "**Modular system**" allows changes and improvements to be made within a single module.

Providentia cPTS v2.0 (coming Q1 2026)

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Providentia's cPTS model

A logistic regression model

$$\ln(\textbf{cPTS} / (1 - \textbf{cPTS})) = X_{DEV} + X_{STE\text{-}A}X_{STE\text{-}B}X_{STE\text{-}C} + \square_{DCE}X_{DCE} + \ldots + \square_{TOR}X_{TOR}$$

which consists of three key components:

- X_{DEV} = starting cPTS † based on **Development Approach (DEV)**
- $X_{STE\text{-}A}X_{STE\text{-}B}X_{STE\text{-}C}$ = change in cPTS † due to **Strength of Treatment Effect (STE)**
  - Magnitude of Treatment Effect (STE-A)
  - Sample Size of Prior Evidence (STE-B)
  - Source of Prior Evidence (STE-C)
- $\square_{DCE}X_{DCE} + \ldots + \square_{TOR}X_{TOR}$ = change in cPTS † due to **remaining risk factors**

† log-odds scale

Relationship between reference assumption, DDCP, & cPTS

Concept (probability *p*)	Log-odds (log(*p* / (1-*p*)))
Reference assumption	X_{DEV}
Providentia DDCP	$X_{DEV} + X_{STE\text{-}A}X_{STE\text{-}B}$
Providentia DDCP, adjusted for source of prior evidence	$X_{DEV} + X_{STE\text{-}A}X_{STE\text{-}B}X_{STE\text{-}C}$
Providentia cPTS	$X_{DEV} + X_{STE\text{-}A}X_{STE\text{-}B}X_{STE\text{-}C} + \square_{DCE}X_{DCE} + \ldots + \square_{TOR}X_{TOR}$

cPTS = DDCP + other risk factors

Development Approach (DEV)

$$\ln(\mathbf{cPTS} / (1 - \mathbf{cPTS})) = \mathbf{X_{DEV}} + X_{STE\text{-}A}X_{STE\text{-}B}X_{STE\text{-}C} + \square_{DCE}X_{DCE} + \ldots + \square_{TOR}X_{TOR}$$

Development Approach (DEV)

User-interface

Development Approach (DEV)

Behind-the-scenes

Table. Starting cPTS based on DEV and the trial success criteria

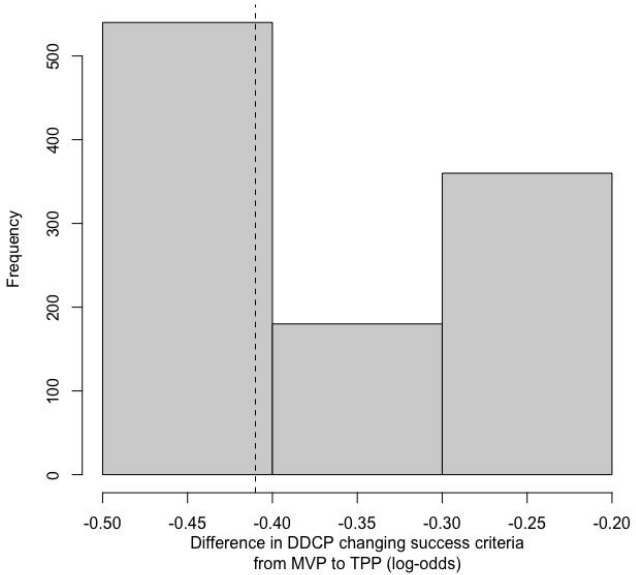
Development Approach	Success = MVP		Success = Target TPP	
	Starting cPTS (probability)	Starting cPTS (log-odds; X_{DEV})	Starting cPTS (probability)	Starting cPTS (log-odds; X_{DEV})
Accelerated	30%	-0.85	22%	-1.27
Classical	50%	0.00	40%	-0.41
Upside	60%	0.41	50%	0.00

Development Approach (DEV)

Rationale

- **MVP:** Starting cPTS's of **30%/50%/60%** are based on **historical probabilities** (at Roche and across the industry) to move from Ph3 to regulatory submission. The decision to tie these cPTS values to achieving the MVP (as opposed to the target TPP) is based on …
  - achieving MVP as a min. requirement for Ph3 success
  - past tendency at Roche to overestimate cPTS by ~10%

- **TPP:** Log-odds of cPTS w.r.t. TPP is defined to be approximately **0.41** less than the log-odds of cPTS w.r.t. MVP. This fixed adjustment results in cPTS values that are easy to recall and apply: **22%/40%/50%**. It also falls within the typical range of difference in DDCP one might expect to see when changing success criteria from MVP to target TPP, assuming a weakly informative prior (see Figure).

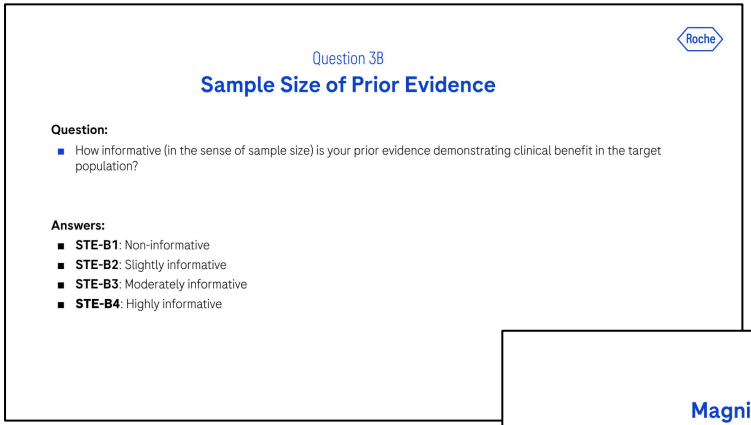


Strength of treatment effect (STE)

$$\ln(\mathbf{cPTS} / (1 - \mathbf{cPTS})) = X_{DEV} + X_{STE\text{-}A}X_{STE\text{-}B}X_{STE\text{-}C} + \square_{DCE}X_{DCE} + \cdots + \square_{TOR}X_{TOR}$$

Strength of treatment effect (STE)

User-interface



Question 3B

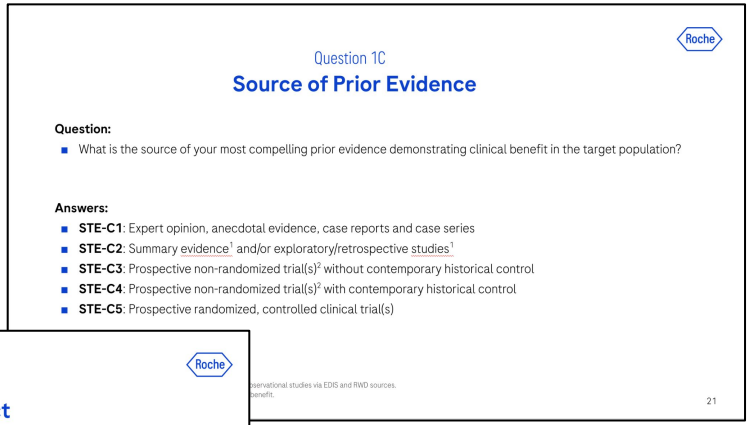
Sample Size of Prior Evidence

Question:

- How informative (in the sense of sample size) is your prior evidence demonstrating clinical benefit in the target population?

Answers:

- **STE-B1**: Non-informative
- **STE-B2**: Slightly informative
- **STE-B3**: Moderately informative
- **STE-B4**: Highly informative



Question 1C

Source of Prior Evidence

Question:

- What is the source of your most compelling prior evidence demonstrating clinical benefit in the target population?

Answers:

- **STE-C1**: Expert opinion, anecdotal evidence, case reports and case series
- **STE-C2**: Summary evidence[1] and/or exploratory/retrospective studies[1]
- **STE-C3**: Prospective non-randomized trial(s)[2] without contemporary historical control
- **STE-C4**: Prospective non-randomized trial(s)[2] with contemporary historical control
- **STE-C5**: Prospective randomized, controlled clinical trial(s)

servational studies via EDIS and RWD sources,
benefit.

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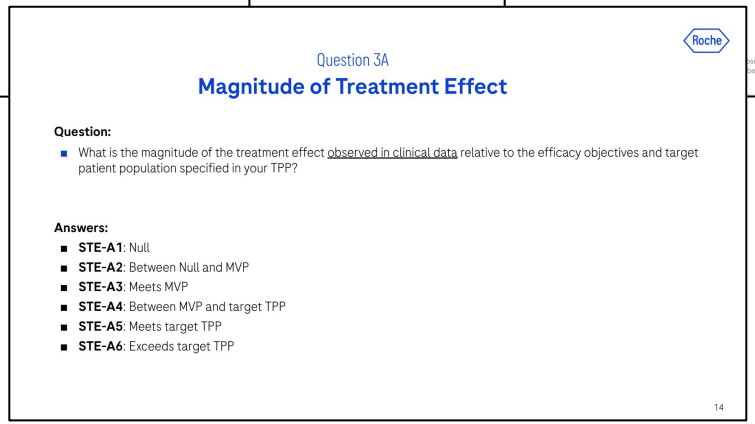

Question 3A

Magnitude of Treatment Effect

Question:

- What is the magnitude of the treatment effect observed in clinical data relative to the efficacy objectives and target patient population specified in your TPP?

Answers:

- **STE-A1**: Null
- **STE-A2**: Between Null and MVP
- **STE-A3**: Meets MVP
- **STE-A4**: Between MVP and target TPP
- **STE-A5**: Meets target TPP
- **STE-A6**: Exceeds target TPP

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Strength of treatment effect

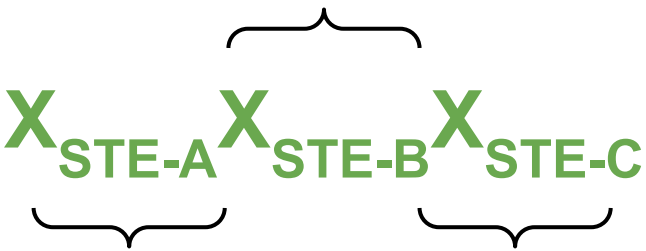
Behind-the-scenes

Change in cPTS one expects to see from incorporating prior evidence via DDCP

Strength of treatment effect

Behind-the-scenes

Percentage retention of max change based on **sample size** of prior evidence [0, 1]



Maximum change in cPTS based on **effect size** of prior evidence [-3, 2]

Percentage retention of max change based on **source** of prior evidence [0.1, 1]

STE-A and STE-B
Rationale

We considered a spectrum of **potential Ph2→Ph3 development scenarios**.

Ph3 study design

- alpha = 0.025 (one-sided)
- beta = (0.1, 0.2)
- Target TPP hazard ratio (HR) = HR under the alternative hypothesis = (0.5, 0.6, …, 0.9)
- MVP HR = minimal detectable difference (MDD)

Reference assumption (initial prior)

- **cPTS = (30%, 50%, 60%) or (22%, 40%, 50%)**
- **# of events = 5% of Ph3**

Clarifies what is the starting cPTS AND mitigates poor small sample size properties of DDCP (see Adv Statistics Boost 8)!

Phase 2 (for updating prior)

- **# of events = (5%, 10%, …, 60%) of Ph3**
- **Observed HR = (“Null”, “Null < x < MVP”, “MVP”, “MVP < x < TPP”, “TPP”, “Exceed TPP”)**

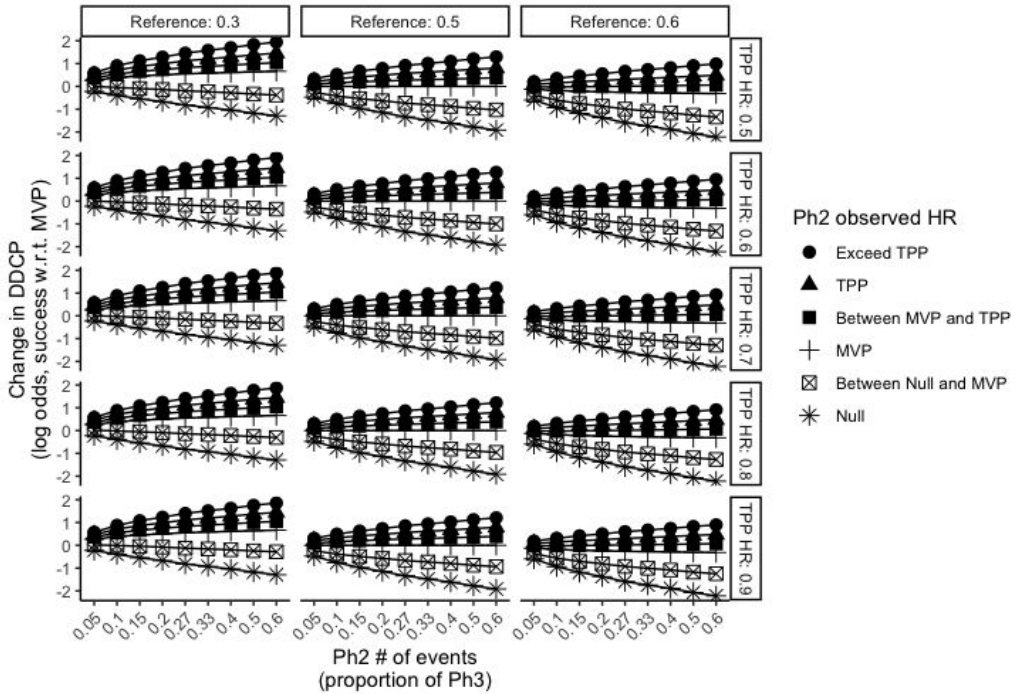
Keep this “variance ratio” in mind for later!

STE-A and STE-B
Rationale

Statistic: change in DDCP (log-odds)

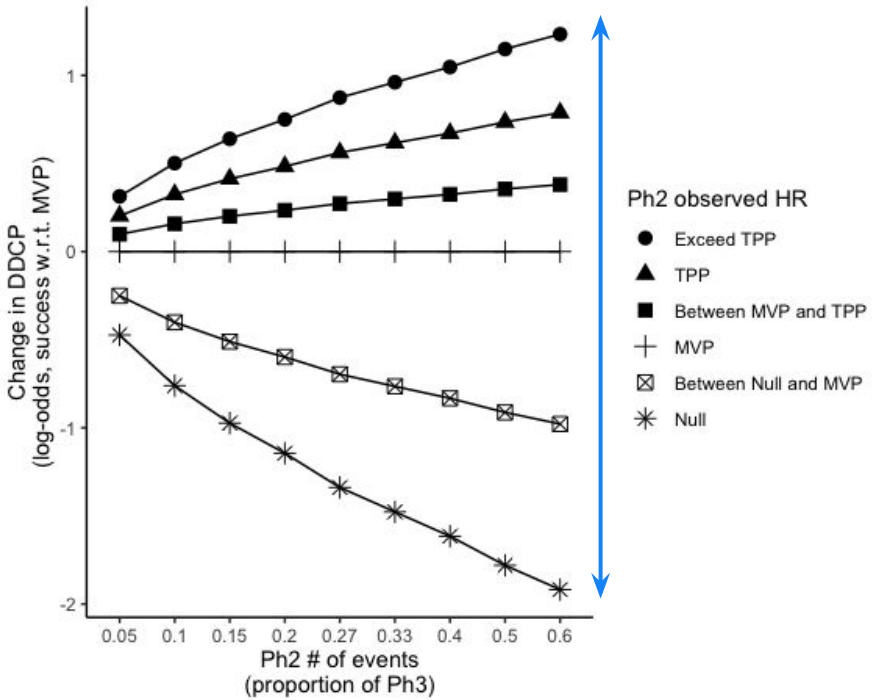
Q: How can we best capture changes across 3240 scenarios?

- Accuracy
- Simplicity
- Generalizability
- Interpretability
- User-interface



STE-A and STE-B
Rationale

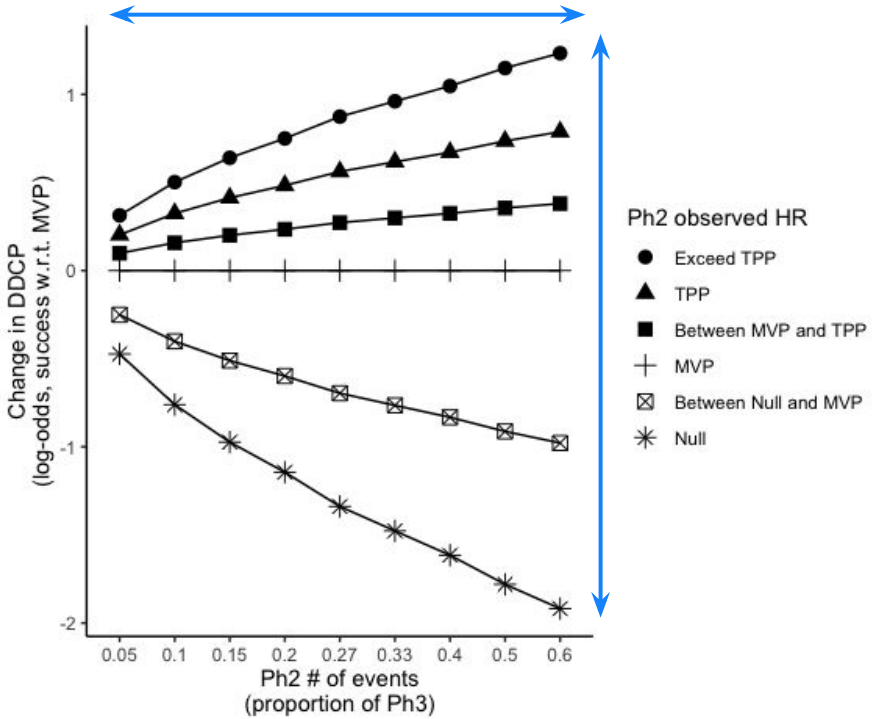
Insight #1: Negative (positive) signal leads to decrease (increase) in cPTS



STE-A and STE-B
Rationale

Insight #1: **Negative (positive) signal** leads to decrease (increase) in cPTS

Insight #2: The larger the **sample size**, the large the decrease or increase in PTS

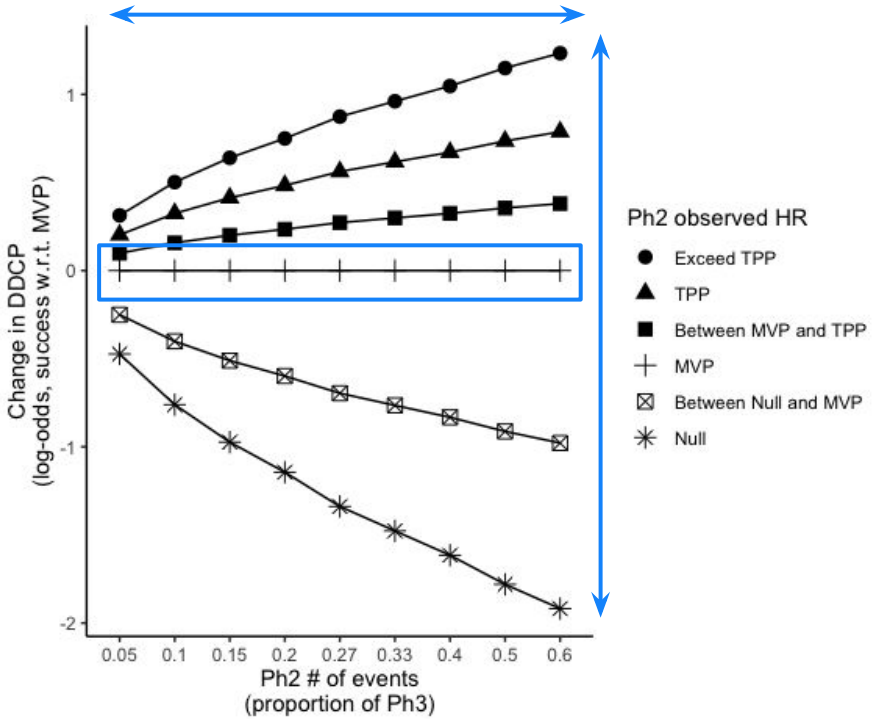


STE-A and STE-B
Rationale

Insight #1: **Negative (positive) signal** leads to decrease (increase) in cPTS

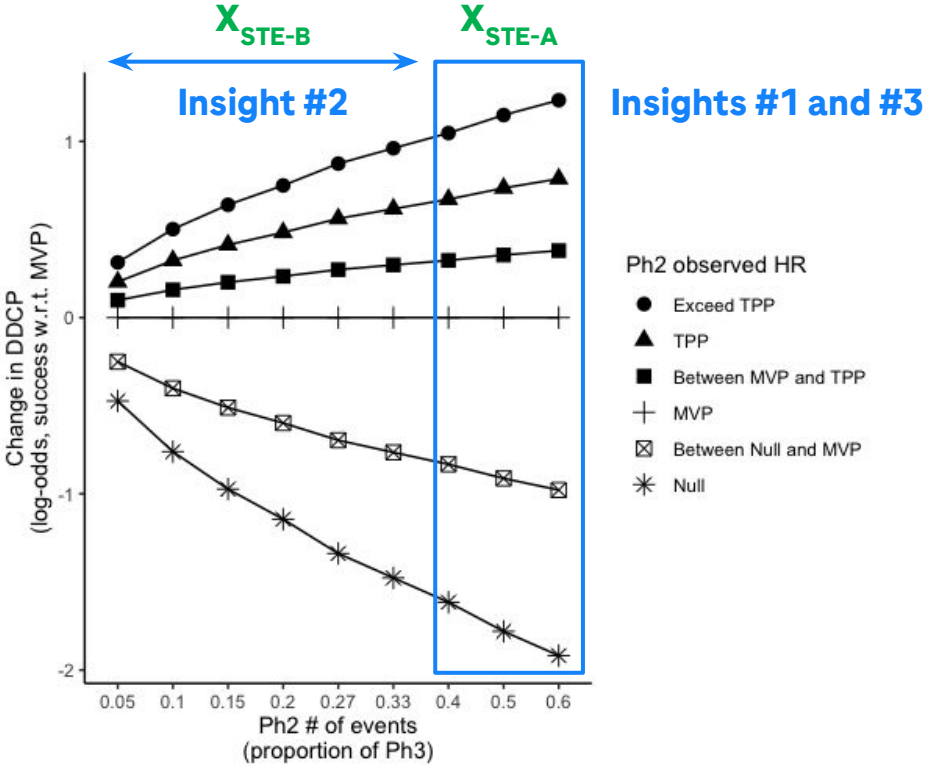
Insight #2: The larger the **sample size**, the large the decrease or increase in PTS

Insight #3: In some cases, prior effect size is **consistent** with the starting cPTS (i.e., Ph2 sample size does not result in further changes of cPTS). When this occurs depends on the reference assumption.



STE-A and STE-B

Rationale



Magnitude of Treatment Effect (STE-A)

Maximum change in cPTS based on Strength of Treatment Effect (STE)

Table. $X_{STE\text{-}A}$ for trial success measure **MVP**

Starting cPTS (DEV)	Magnitude of treatment effect (STE-A)					
	Null (STE-A1)	Null < x < MVP (STE-A2)	MVP (STE-A3)	MVP < x < TPP (STE-A4)	TPP (STE-A5)	>TPP (STE-A6)
30%	-1.2	-0.3	0.6	1.1	1.5	2.1
50%	-1.8	-0.9	0.0	0.4	0.9	1.4
60%	-2.1	-1.2	-0.3	0.1	0.6	1.2

Similar table for trial success measure TPP.

Sample size of prior evidence (STE-B)

Percentage retention of “max change in cPTS”

Table. $X_{STE\text{-}B}$

Sample size of prior evidence (STE-B)			
Non-informative (STE-B1)	Slightly Inf. (STE-B2)	Moderately Inf. (STE-B3)	Highly Inf. (STE-B4)
0%	45%	75%	100%

How is “information” measured?

Comments Q1B

Sample Size of Prior Evidence

(Details for Biostatisticians)

Given a prior distribution for the unknown treatment effect, we define its effective sample size (ESS) by relating the **variance of the prior to the variance of the Ph3 effect estimate**. Neuenschwander et al. (2020) refer to this as an information-based approach to measuring ESS. This relationship becomes clear under the principles of maximum likelihood, where Fisher Information is defined as the inverse variance of the maximum likelihood estimate (MLE).

To select an answer, users should, if possible, calculate the **variance ratio** between the Ph3 effect estimate and prior evidence, which intuitively is also the **information ratio**:

$$\frac{\text{Variance of Ph3 effect estimate}}{\text{Variance of prior evidence}} = \frac{\text{Information of prior evidence}}{\text{Information of Ph3 effect estiamate}}$$

The following table can then be used to select the appropriate STE-B category:

Variance ratio	Category
<5%	STE-B1
5-19%	STE-B2
20-39%	STE-B3
40-60%	STE-B4

Examples of variance ratio calculations are included on the next slide. For small Ph3 trials such as in rare diseases, one may instead require a minimum number of, say, 10 patients before considering a prior evidence as "slightly informative" (STE-B2).

Source of prior evidence (STE-C)

Percentage retention of “max change in cPTS”

Table. $X_{STE\text{-}C}$

Source of prior evidence (STE-C)				
Expert opinion, anecdotal evidence, case reports and case series	Summary evidence and exploratory/retrospective studies	Prospective non-randomized trial(s) without contemporary historical control	Prospective non-randomized trial(s) with contemporary historical control	Prospective randomized, controlled clinical trial(s)
(STE-C1)	(STE-C2)	(STE-C3)	(STE-C4)	(STE-C5)
10%	25%	50%	75%	100%

STE-C
Rationale

STE-C is included as an additional **interaction term** so that its impact **mimics that of STE-B**: the higher quality the source of data, the more robust we can consider the change in cPTS based on STE-A to be.

The actual percentages were **subjectively chosen** with a specific goal in mind: to reflect in the most extreme cases a **+/- 10% cPTS** due to having **prospective non-randomized trial (STE-C3) vs. prospective randomized controlled trial (STE-C5)**.

Intuitively, 50% retention for STE-C3 can be interpreted as discounting the sample size of a prospective non-randomized trial by 75%. In other words, 4 patients from a prospective non-randomized trial are equivalent to 1 patient from a prospective randomized controlled trial.

Remaining risk factors

$$\ln(\mathbf{cPTS} / (1 - \mathbf{cPTS})) = X_{DEV} + X_{STE\text{-}A} X_{STE\text{-}B} X_{STE\text{-}C} + \square_{DCE} X_{DCE} + \ldots + \square_{TOR} X_{TOR}$$

Remaining risk factors

User-interface

Remaining risk factors

Behind-the-scenes

Risk factor	□	X			
		Level 1	Level 2	Level 3	Level 4
Disconfirmatory Evidence (DCE)	0.26	-1.78	0.00	–	–
Target Involvement in the Disease (TLD)	0.03	-1.75	-0.50	1.90	–
Mechanism of Action (MOA)	0.03	-1.73	-0.38	1.86	–
Single-Agent Activity (SAA)	0.16	-1.47	-0.76	1.53	0.00
Target Dose and Schedule (TDS)	0.08	-1.98	-0.49	1.45	–
Safety Profile Assessment (SPA)	0.33	-2.12	-0.51	0.00	–
CMC Risk (CMC)	0.17	-1.37	0.00	–	–

Remaining risk factors

Behind-the-scenes

Risk factor	□	X			
		Level 1	Level 2	Level 3	Level 4
Primary Endpoint Assessment (PEA)	0.19	-1.90	0.00	–	–
Primary Endpoint Change (PEC)	0.14	-1.92	-0.04	0.00	–
Patient Population Risk (PPR)	0.23	-1.63	–	–	–
Biomarker for Patient Selection (BPS)	0.01	-1.38	-1.00	1.67	0.00
Trial Design Risk (TDR)	0.11	-1.22	0.00	1.10	–
Trial Operational Risk (TOR)	0.12	-1.12	0.00	–	–

Remaining risk factors

Rationale

To derive **X**, SMEs were asked to weigh the various levels' ordinal effects using a 7-Point Likert-scale:

7-Point Likert Scale Feature Impact Weight on the Overall Clinical PTS						
(-3) Highly Significant Negative Impact	(-2) Significant Negative Impact	(-1) Negative Impact	(0) No Impact	(+1) Positive Impact	(+2) Significant Positive Impact	(+3) Highly Significant Positive Impact

The average weights across SMEs were then taken as the covariate values **X**:

Example of Weighting Outcome for 2 Features: TLD and MOA

Acronym	Feature Code	Feature Description	Mean	Data Bar Representation of Feature Weights
TLD (Target Link to Disease)	TLD1	**TLD1:** Limited understanding of the role of the target/pathway in the underlying disease pathophysiology and/or positive pre-clinical data only.	-1.75	-1.75
	TLD2	**TLD2:** Positive signals from retrospective analyses of clinical study and/or clinical case study reports, without prospective clinical evidence.	-0.50	-0.50
	TLD3	**TDL3:** Positive pre-clinical data and/or scientific support, with prospective clinical evidence.	1.38	1.38
MOA (Mechanism of Action)	MOA1	**MOA1:** Limited understanding of the drug's MoA and/or positive pre-clinical data only.	-1.50	-1.50
	MOA2	**MOA2:** Positive signals from retrospective/exploratory analyses of clinical datasets, without prospective clinical evidence.	-0.38	-0.38
	MOA3	**MOA3:** Positive pre-clinical and/or scientific support, with prospective clinical evidence.	1.25	1.25

Remaining risk factors

Rationale

To derive □, PSM created 78 scenarios (i.e., various combination of risk factors) that were thought to be typical of Roche clinical Ph3 programs. A ridge logistic regression was then fit using expected PTS as the outcome, DEV and STE as offsets, and risk factors as the covariates **X**. The estimated model coefficients became the risk factor weights □ for future predictions.

SCENARIO NUMBER	Example of 9 PCS SCENARIOS	PPP Exp PTS
1	TLD3-MOA3-SPE4-STE1-SAA2-DCE2-PEA2-PEC2-PPC2-SBRNA-TDR2-TOC2-TDS1-SPR1-TFR2	30%
2	TLD2-MOA2-SPE4-STE1-SAA1-DCE2-PEA2-PEC2-PPC1-SBR2-TDR2-TOC2-TDS1-SPR2-TFR1	10%
3	TLD2-MOA2-SPE2-STE1-SAANA-DCE2-PEA2-PEC3-PPC1-SBRNA-TDR2-TOC2-TDS2-SPR2-TFR1	14%
4	TLD2-MOA2-SPE2-STE1-SAANA-DCE1-PEA1-PEC3-PPC2-SBRNA-TDR2-TOC2-TDS1-SPR3-TFR2	7%
5	TLD3-MOA3-SPE4-STE2-SAANA-DCE2-PEA2-PEC3-PPC2-SBR3-TDR2-TOC2-TDS3-SPR3-TFR2	55%
6	TLD1-MOA3-SPE2-STE1-SAANA-DCE1-PEA1-PEC3-PPC2-SBR2-TDR2-TOC2-TDS3-SPR2-TFR2	12%
7	TLD3-MOA3-SPE4-STE2-SAA2-DCE2-PEA2-PEC2-PPC2-SBRNA-TDR2-TOC2-TDS2-SPR2-TFR2	47%
8	TLD2-MOA2-SPE2-STE1-SAANA-DCE2-PEA1-PEC3-PPC1-SBRNA-TDR2-TOC2-TDS3-SPR2-TFR2	20%
9	TLD1-MOA3-SPE2-STE1-SAANA-DCE2-PEA1-PEC3-PPC2-SBR2-TDR2-TOC2-TDS3-SPR2-TFR2	17%

Providentia in action

Calculating Providentia cPTS

Step 1. Multiply

Risk factor	β	Team selection	X	Risk contribution βX
Development approach (DE)	1.00	Classical	-0.41	-0.41
Strength of treatment effect (STE)	1.00	STE-A5 STE-B2 STE-C3	(0.3 x 0.45 x 0.50)	0.07
Target involvement in disease (TID)	0.03	TID3	1.90	0.06
Mechanism of action (MOA)	0.03	MOA3	1.86	0.05
⋮	⋮	⋮	⋮	⋮
CMC Risk (CMC)	0.17	CMC1	-1.37	-0.23

Step 2. Add

Step 3. Convert

cPTS (log-odds)	-0.96
cPTS (probability)	**28%**

Calculating cPTS directly from DDCP

How?

Step 1. Define an initial prior distribution for DDCP such that (A) the prior sample size equals to 5% of the Ph3 study, and (B) the resulting DDCP equals the desired reference assumption:

$$\ln(\textbf{initial DDCP} / (1 - \textbf{initial DDCP})) = X_{DEV}$$

The required prior mean may be calculated either analytically or through trial-and-error. For more information, including how to implement this step and why this step is generally recommended for all DDCP calculations, see Advanced Statistics Boost 8 on "DDCP: what and how?".

Step 2. Update initial prior with whatever prior evidence is available and re-calculate DDCP. Denote by **Δ** the log-odds difference between the updated and initial DDCP:

$$\Delta = \ln(\textbf{DDCP}/(1-\textbf{DDCP})) - X_{DEV}$$

Step 3. In the Providentia cPTS equation, replace $X_{STE\text{-}A}X_{STE\text{-}B}$ by **Δ**:

$$\ln(\textbf{cPTS} / (1 - \textbf{cPTS})) = X_{DEV} + \Delta X_{STE\text{-}C} + \square_{DCE}X_{DCE} + \ldots + \square_{TOR}X_{TOR}$$

Calculating cPTS directly from DDCP

How? (In the special case that prior is based on a randomized study)

Step 1. Define an initial prior distribution for DDCP such that (A) the prior sample size equals to 5% of the Ph3 study, and (B) the resulting DDCP equals the desired reference assumption:

$$\ln(\textbf{initial DDCP} / (1 - \textbf{initial DDCP})) = X_{DEV}$$

The required prior mean may be calculated either analytically or through trial-and-error. For more information, including how to implement this step and why this step is generally recommended for all DDCP calculations, see Advanced Statistics Boost 8 on "DDCP: what and how?".

Steps 2-3. Update initial prior with whatever prior evidence is available and re-calculate DDCP. **If prior evidence is based on randomized data (STE-C4)**, then

$$\ln(\textbf{cPTS} / (1 - \textbf{cPTS})) = \ln(\textbf{DDCP}/(1-\textbf{DDCP})) + \square_{DCE}X_{DCE} + \ldots + \square_{TOR}X_{TOR}$$

The following examples focus on the first two risk factors of Providentia, **Development Approach (DEV)** and **Strength of Treatment Effect (STE)**. The purpose here is to illustrate how Providentia updates a reference assumption by incorporating clinical evidence and how this process is similar and different from DDCP.

Astegolimab ALIENTO & ARNASA studies

Press release

[Ad hoc announcement pursuant to Art. 53 LR] Roche provides update on astegolimab in chronic obstructive pulmonary disease

Basel, 21 July 2025 - Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today topline results from the pivotal phase IIb ALIENTO (n=1,301) and the phase III ARNASA (n=1,375) trials investigating astegolimab compared to placebo, on top of standard of care maintenance therapy in people with moderate to very severe chronic obstructive pulmonary disease (COPD). The studies included a broad population: both former and current smokers, regardless of blood eosinophil count, who have a history of frequent exacerbations.

The pivotal phase IIb ALIENTO study met its primary endpoint and showed that astegolimab reduced the annualised exacerbation rate (AER) by a statistically significant 15.4% at 52 weeks, when given every two weeks. However, the phase III ARNASA study did not meet its primary endpoint of a statistically significant reduction in the AER, demonstrating a numerical 14.5% reduction, at 52 weeks when astegolimab was given every two weeks. The results were generally consistent across secondary endpoints in both studies. The total number of exacerbations was lower than prospectively anticipated in both trials. The safety profile of astegolimab was consistent with previously reported data, with no new safety signals identified.

Astegolimab ALIENTO & ARNASA studies

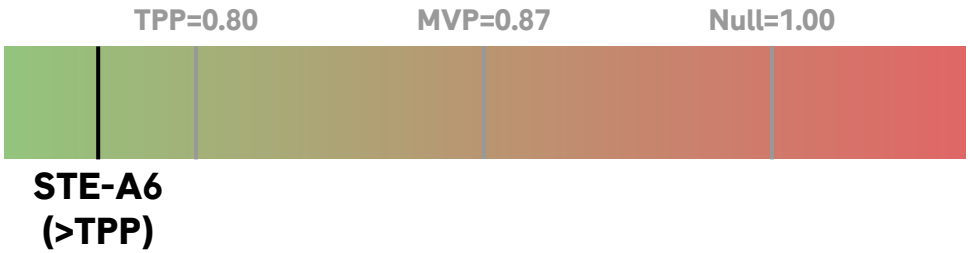
Ph3 design and evidence prior to readout

	Ph3 study ALIENTO/ARNASA	Prior evidence COPD-ST2OP
Population	COPD	COPD
Treatment	Astegolimab vs. Placebo	Astegolimab vs. Placebo
Endpoint	AERR	AERR
Sample size	860 patients	81 patients
Result	?	AERR = 0.78 (0.53, 1.14)

Astegolimab ALIENTO & ARNASA studies

STE-A

Prior AERR estimate = **0.78**



Astegolimab ALIENTO & ARNASA studies

STE-B

Variance ratio estimate #1:

- Ph3 sampling variance for ln(AERR) = 0.00477
- Prior variance for ln(AERR) based on 95% CI = $[(\ln(1.14) - \ln(0.53)) / 1.96 / 2]^2$ = 0.0382
- Variance ratio = 0.00477 / 0.0382 = **13%**

Variance ratio estimate #2:

- Ph3 sample size = 430 astegolimab, 430 placebo
- Prior sample size = 42 astegolimab, 39 placebo
- Variance ratio = (1/430 + 1/430) / (1/42 + 1/39) = **9%**

Astegolimab ALIENTO & ARNASA studies

DDCP and cPTS

DDCP w.r.t. MVP (AERR ≤ 0.87): 67%

DDCP w.r.t. TPP (AERR ≤ 0.80): 47%

Risk factor	Selections	Impact on cPTS w.r.t. MVP (log-odds)	Impact on cPTS w.r.t. TPP (log-odds)	Rationale
DEV	Classical	0.00	-0.41	
Ref. assumption (%)		0.00 (50%)	-0.41 (40%)	

Astegolimab ALIENTO & ARNASA studies

DDCP and cPTS

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Risk factor	Selections	Impact on cPTS w.r.t. MVP (log-odds)	Impact on cPTS w.r.t. TPP (log-odds)	Rationale
DEV	Classical	0.00	-0.41	
STE	STE-A6 STE-B2	+1.40 x0.45	+0.80 x0.45	Ph2 COPD-ST2OP study with 81 patients suggests AERR = 0.78 (0.53, 1.14)
Providentia "DDCP" (%)		0.63 (65%)	-0.05 (49%)	Providentia DDCP is similar to DDCP

Astegolimab ALIENTO & ARNASA studies

DDCP and cPTS

DDCP w.r.t. MVP (AERR ≤ 0.87): 67%

DDCP w.r.t. TPP (AERR ≤ 0.80): 47%

Risk factor	Selections	Impact on cPTS w.r.t. MVP (log-odds)	Impact on cPTS w.r.t. TPP (log-odds)	Rationale
DEV	Classical	0.00	-0.41	
STE	STE-A6 STE-B2 STE-C5	+1.40 x0.45 x1.00	+0.80 x0.45 x1.00	Ph2 COPD-ST2OP is a randomized study comparing astegolimab vs. placebo
Providentia “DDCP”, adjusted for source (%)		0.63 (65%)	-0.05 (49%)	Given a prior prospective randomized study, Providentia DDCP adjusted for source is similar to DDCP

Lunsumio + Polivy SUNMO study

Press release

Roche's Lunsumio and Polivy combination significantly prolongs remission for people with relapsed or refractory large B-cell lymphoma

Basel, 20 June 2025 - Roche (SIX: RO, ROG; OTCQX: RHHBY) presented today results from the phase III SUNMO [NCT05171647] study showing Lunsumio® (mosunetuzumab) administered subcutaneously in combination with Polivy® (polatuzumab vedotin) demonstrated a clinically meaningful and statistically significant improvement in its primary endpoints of progression-free survival (PFS) and objective response rate (ORR) compared to MabThera®/Rituxan® (rituximab), gemcitabine and oxaliplatin (R-GemOx), in people with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) who are not eligible for transplant.[1] Primary analysis data were featured at the 18th International Conference on Malignant Lymphoma as a late-breaking oral presentation.

At a median follow-up of 23.2 months, the Lunsumio and Polivy combination demonstrated a 59% reduction in risk of disease progression or death compared to R-GemOx (hazard ratio [HR] 0.41, 95% confidence interval [CI]: 0.28–0.61; p<0.0001).[1] Median PFS was three times longer with Lunsumio and Polivy at 11.5 months (95% CI: 5.6-17.6), compared to 3.8 months for R-GemOx (95% CI: 2.9-4.1) and 12-month PFS was more than doubled at 48.5% (95% CI: 39.6-57.4) vs.17.8% (95% CI: 5.4-30.3), respectively. This PFS benefit was consistent across subgroups, including in high-risk patients with primary refractory disease (HR 0.46, 95% CI: 0.29–0.72).[1] At the interim analysis, overall survival (OS) data were not yet mature. OS numerically favoured the Lunsumio and Polivy combination with a median of 18.7 months (95% CI: 14.1–not evaluable [NE]) compared to 13.6 months for R-GemOx (95% CI: 9.9–NE; HR 0.80; 95% CI: 0.54 - 1.20).[1]

Lunsumio + Polivy SUNMO study

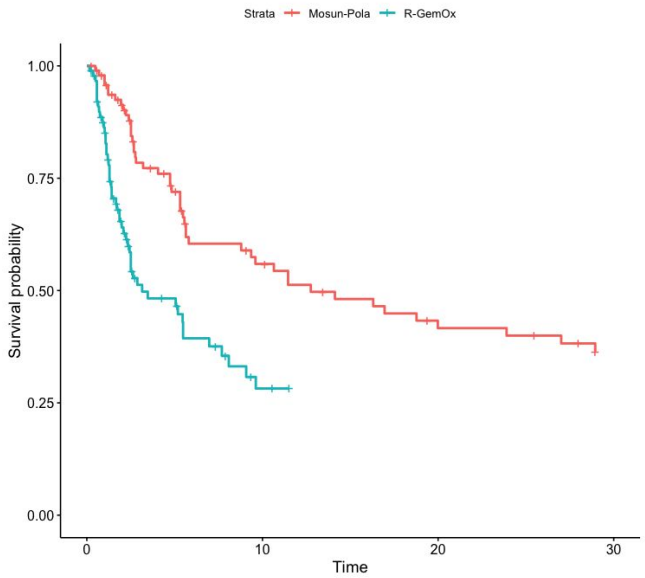
Ph3 design and evidence prior to readout

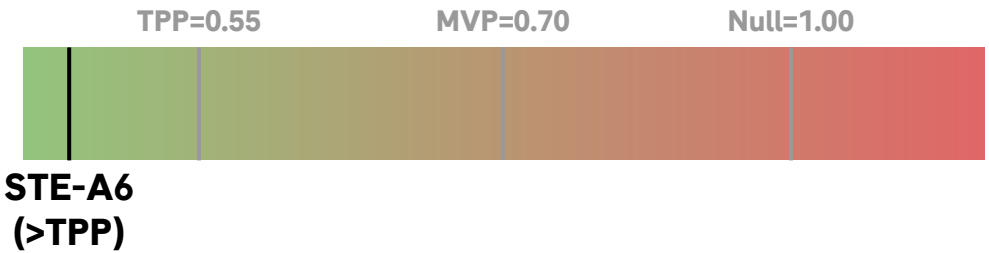
	Ph3 study	Prior evidence	
	SUNMO	GO40516	STARGLO
Population	R/R aNHL	R/R DLBCL	R/R DLBCL
Treatment	Mosun+Pola vs. R-GemOx	Mosun+Pola	R-GemOx
Endpoint	PFS HR	PFS, Kaplan-Meier	PFS, Kaplan-Meier
Sample size	133 events	49 events	38 events
Result	?	PFS HR = 0.43 (0.28, 0.65)	

Lunsumio + Polivy SUNMO study

STE-A

Prior HR estimate = **0.43**





Lunsumio + Polivy SUNMO study

STE-B

Variance ratio estimate:

- Ph3 sample and event size = 222 patients randomized 2:1, 133 events
- Prior event size by arm = 49 Mosun+Pola, 38 R-GemOx
- Variance ratio = (1/ (⅔ x 133) + 1/(⅓ x 133)) / (1/49 + 1/38) = **72%**

How to adjust/penalize for cross-trial comparison?

Lunsumio + Polivy SUNMO study

DDCP and cPTS

DDCP w.r.t. MVP (HR ≤ 0.70): 94%

DDCP w.r.t. TPP (HR ≤ 0.55): 78%

Risk factor	Selections	Impact on cPTS w.r.t. MVP (log-odds)	Impact on cPTS w.r.t. TPP (log-odds)	Rationale
DEV	Upside	0.41	0.00	Large molecule NME
Ref. assumption (%)		0.41 (60%)	0.00 (50%)	

Lunsumio + Polivy SUNMO study

DDCP and cPTS

DDCP w.r.t. MVP (HR ≤ 0.70): 94%

DDCP w.r.t. TPP (HR ≤ 0.55): 78%

Risk factor	Selections	Impact on cPTS w.r.t. MVP (log-odds)	Impact on cPTS w.r.t. TPP (log-odds)	Rationale
DEV	Upside	0.41	0.00	
STE	STE-A6 STE-B4	+1.20 x1.00	+0.50 x1.00	Prior evidence based on 87 events (49 Mosun+Pola, 38 R-GemOx) suggests PFS HR = 0.43 (0.28, 0.65)
Providentia "DDCP" (%)		1.61 (83%)	0.50 (62%)	Due to categorization of impact, Providentia can under-/over-estimate DDCP in extreme cases

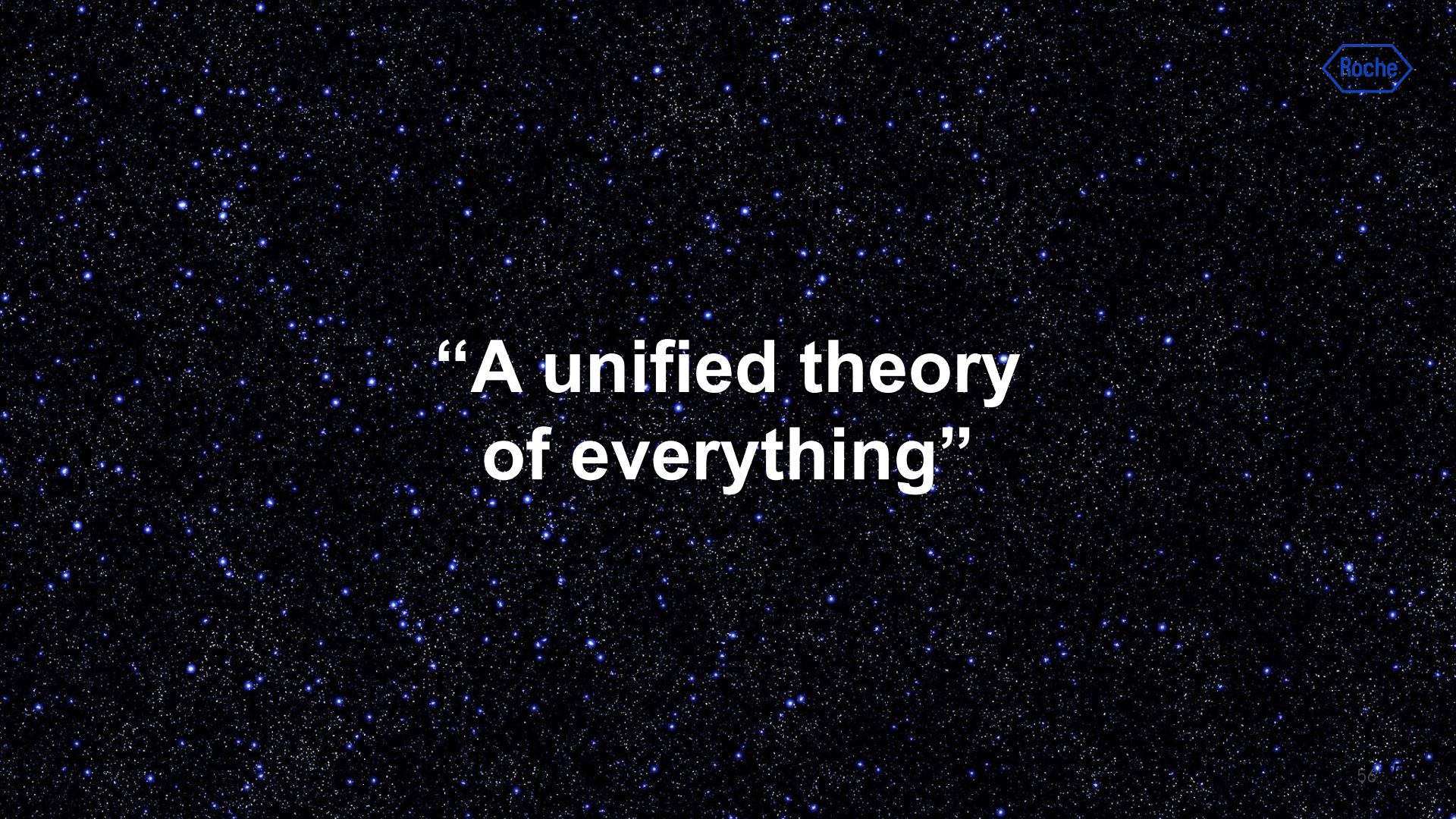
Lunsumio + Polivy SUNMO study

DDCP and cPTS

DDCP w.r.t. MVP (HR ≤ 0.70): 94%

DDCP w.r.t. TPP (HR ≤ 0.55): 78%

Risk factor	Selections	Impact on cPTS w.r.t. MVP (log-odds)	Impact on cPTS w.r.t. TPP (log-odds)	Rationale
DEV	Upside	0.41	0.00	
STE	STE-A6 STE-B4 STE-C4	+1.20 x1.00 x0.75	+0.50 x1.00 x0.75	Prior evidence is based on a cross-trial comparison of GO40516 vs. STARGLO
Providentia "DDCP", adjusted for source (%)		1.31 (79%)	0.38 (59%)	Unlike traditional DDCP, Providentia discounts clinical evidence based on its source/quality


“A unified theory
of everything”

Providentia cPTS v2.0

- **Clear contribution** of reference assumption, prior data, and other risk factors.
  - **Clear relationship** between reference assumption, DDCP, and final cPTS.

- **Unified** yet **flexible** framework:
  - DDCP is not required to calculate Providentia cPTS.
  - However, if DDCP is available, then it can (A) inform selection of Providentia risk factors, or (B) be directly combined with other risk factors to calculate a Ph3 cPTS.

- "**Modular system**" allows changes and improvements to be made within a single module.

How can biostatisticians show up?

1. Ask **"Where are we currently?"** Based on the current development of this molecule (and forgetting for a moment the actual clinical data that has been observed), where do we find ourselves in terms of cPTS?
   - High risk? Medium risk? Low risk?

2. Ask **"What is our clinical data telling us?"**
   - STE-A: What is the estimated effect size?
   - STE-B: How informative is this estimate? Is it based on a large or small sample size?
   - STE-C: How reliable is this source of clinical data?

   Note the importance of **bridging gaps in evidence** (treatment, population, endpoints, etc.)!

3. **Understand** the relationships between these factors and help teams to **navigate** through them.

Resource Links

Material	Link	Audience	Contacts
cPTS training deck		GDLs, Portfolio leads, PMs, PTLs, BDPLs	Marisa Bottarelli (PD PSM)
rPTS training deck		GRLs	Ana Maria Buehlmann (PDR) for content Anne Madej (PDR) for technical questions/access
FAQ		All users	Marisa Bottarelli (PD PSM)
Technical overview		Technical experts / PDD	Godwin Yung (PDD) & Shaun Comfort (PDS)

Providentia gSite

Webtool: **providentia.roche.com**
(VPN required)