PK-PD Analysis of PASI with Data at Boundary: BI 655066, an Anti-IL-23A mAb for the Treatment of Psoriasis

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Introduction

- Psoriasis is the most prevalent immune-mediated skin disease, affecting 2% of the world population: 25 million in North America and Europe.
- In clinical trials, disease activity is measured using the Psoriasis Area and Severity Index (PASI) for 4 body regions, based on area and severity of redness (erythema), scaling (desquamation) and thickness (induration), from 0 to 72 points.
- BI 655066 is a humanized monoclonal antibody that inhibits the action of IL-23 on all cells of the IL-23 axis, which include Th17, Th22, and innate lymphoid cells responsible for inflammation and abnormal keratinocyte proliferation of psoriatic plaques.

PMX/Statistical Considerations

- PK-PD analyses of PASI data have addressed the lag between the dynamics of psoriatic lesions and drug concentrations.[1–3]
- PASI scores are bound, with high variability around the mean and decreasing variability at the extremes similar to ADAS cog data for which beta regression has been implemented in NONMEM.[4]
- PASI data from the completed initial dose-ranging study in patients (1311.1) and data over at least 24 weeks of treatment from an ongoing dose-ranging study vs. a comparator, ustekinumab (1311.2), were used. The dataset disposition is depicted in **Table 1**.
- 2 CM adequately describes the PK of BI 655066; CL and Vss comparable to other mAbs binding soluble targets, linear with respect to dose and time with BWT as a significant predictor.
- Individual level estimates of BI 655066 PK were used to predict concentrations of BI 655066 inhibiting PASI formation.
- Ustekinumab PK were not assayed in study 1311.2 and were assumed to be that of BI 655066, given the similar PK properties of the two compounds. A parameter accounting for potency difference between ustekinumab and BI 655066 was included.

Table 1A. PK-PD dataset and 1311.1 study

Study 1 (n=39)	Placebo (IV or SC)	0.01 mg/kg (IV)	0.05 mg/kg (IV)	0.25 mg/kg (IV)	1 mg/kg (IV)	3 mg/kg (IV)	5 mg/kg (IV)	0.25 mg/kg (SC)	1 mg/kg (SC)
Number of Patients	8	3	3	3	3	3	3	7	6
Body Weight, kg (range)	108 (68–128)	90 (78–121)	105 (93–107)	92 (76–117)	91 (88–97)	88 (88–92)	81 (47–109)	82 (47–117)	85 (59–113)
Age, years (range)	51 (30–70)	49 (42–55)	46 (37–54)	46 (26–47)	38 (34–47)	45 (33–51)	34 (29–39)	50 (24–61)	40 (28–58)
Sex, Female/Male	2/6	1/2	1/2	1/2	0/3	0/3	0/3	1/6	2/4
PK Samples/ subject (range)	NA	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	9 (7–10)	9 (9–17)	14 (12–17)
PD Samples/ subject (range)	11 (10–14)	11 (11–11)	11 (11–11)	11 (11–11)	11 (11–11)	11 (11–11)	10 (8–11)	11 (11–19)	16 (14–19)

Table 1B. PK-PD dataset and 1311.2 study

Study 2 (n=166)	18 mg (SC)	90 mg (SC)	180 mg (SC)	45 mg (SC) ustekinumab	90 mg (SC) ustekinumab
Number of Patients	43	41	42	28	12
Body Weight, kg (range)	95 (57–138)	89 (50–136)	87 (49–134)	85 (55–99)	107 (100–129)
Age, years (range)	45 (20–69)	51 (24–70)	46 (22–72)	42 (26–69)	44 (35–66)
Sex, Female/Male	20/23	10/18	11/30	3/9	13/29
PK Samples/ subject (range)	11 (3–15)	12 (8–15)	13 (4–15)	NA	NA
PD Samples/ subject (range)	13 (5–17)	15 (10–17)	15 (6–17)	14 (11–17)	13 (10–17)

Methods

- PASI score data were normalized to a zero-to-one scale and modeled using a form of beta regression with modification in the residual likelihood to accommodate observations at zero, the lower boundary of the scale.
- Model parameters Emax and a placebo drug effect multiplicatively modify the kin parameter.
- Current analysis represents an adaptation of the beta regression methodology from the recent publication of Xu et al. to data with scores at the boundary.[4]

Augmented Beta Distribution

- In general, one may define a 0–1 augmented Beta $(\alpha, \beta, p_0, p_1)$ distribution as one with density:

$$p(x) = \begin{cases} p_0 : x = 0 \\ p_1 : x = 1 \\ (1 - p_0 - p_1)\ \dfrac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\,\Gamma(\beta)}\ x^{\alpha-1}\,(1-x)^{\beta-1} : 0 < x < 1 \end{cases}$$

- In our application, we assume that the same conditions that make *low*-valued responses (or high-valued responses, respectively) likely also make *zero*-valued (or one-valued, respectively) responses likely. It therefore makes sense for p_0 and p_1 to be a function of $\mu = \alpha/(\alpha+\beta)$. One approach is to let:

$$p_0 = f_0(\mu) = \text{logit}^{-1}(-\gamma_0 - \gamma_1 \cdot \text{logit}(\mu))$$
$$p_1 = f_1(\mu) = \text{logit}^{-1}(-\gamma_0 - \gamma_1 \cdot \text{logit}(\mu))$$

- Other choices for f_0 and f_1 are possible, as long as they force the condition $p_0 + p_1 \leq 1$.
- As parameterized above, f_0 and f_1 offer flexibility as a function of γ_0 and γ_1 ranging from nearly pure beta distribution to a nearly pure binomial distribution with a variety of intermediate possibilities.

Implementation in NONMEM

```
NCOMPARTMENTS=4
$PK; individual PK estimates (PK model, sequential PK-PD, not shown)
;PD PARAMS
SMAX=72
LBAS = THETA(8) + ETA(1)          ; baseline on logit scale
BPRP = EXP(LBAS)/(1+EXP(LBAS))    ; baseline as a proportion
BSCR = SMAX*BPRP                  ; baseline score [0–1]

KOUT= THETA(9)
IC50=THETA(10)                    ; IC50 parameter
EMAX=THETA(11)                    ; Emax on logit scale
IMAX=EXP(EMAX)/(1+EXP(EMAX))      ; asymptotic inhibition as a proportion
GAMMA=THETA(12)                   ; Hill coefficient
TAU=THETA(13)                     ; Beta distribution dispersion param
PBMAX=THETA(14)                   ; placebo response on logit scale
GAMMA0 = EXP(THETA(15))           ;
GAMMA1 = EXP(THETA(16))           ;
A_0(4)=BSCR                       ; initialization
KIN = BSCR * KOUT                 ; initialization

$DES
PLCB = EXP(PBMAX)/(1 + EXP(PBMAX))    ; placebo response as a proportion
INHD = 1 - IMAX*(A(2)/V2**GAMMA)/(IC50+(A(2)/V2**GAMMA))
DADT(1)...DADT(3)                     ; 2 compartment PK model
DADT(4)= KIN*INHD*PLCB - KOUT*A(4)    ; IRM w inhibition of kin (PsO lesions)

$ERROR (OBSERVATION ONLY)
MU = (A(4)) / SMAX                    ; assumes modeling done on (0,SMAX) scale
MULGT = LOG(MU / (1-MU))
P0LGT = - GAMMA0 - GAMMA1*MULGT
P1LGT = - GAMMA0 + GAMMA1*MULGT
P0 = EXP(P0LGT)/(1+EXP(P0LGT))
P1 = EXP(P1LGT)/(1+EXP(P1LGT))

ALPHA=MU*TAU                          ; parameters of the log(gamma) function
BETA=(1-MU)*TAU
X1=ALPHA+BETA
X2=ALPHA
X3=BETA

                  ; approximation of gamma function proposed by Xu et al. (2013)[4]
LG1=0.5*(LOG(2*3.1415)-LOG(X1)) + X1 * (LOG(X1)-1) + (5/4) * X1 * (LOG ( 1 + (1/(15*X1**2))));
LG2=0.5*(LOG(2*3.1415)-LOG(X2)) + X2 * (LOG(X2)-1) + (5/4) * X2 * (LOG ( 1 + (1/(15*X2**2))));
LG3=0.5*(LOG(2*3.1415)-LOG(X3)) + X3 * (LOG(X3)-1) + (5/4) * X3 * (LOG ( 1 + (1/(15*X3**2))));

                  ; Log Likelihood of the 0–1-augmented beta distribution
IF(DV.GT.0.AND.DV.LT.SMAX) LOGL = LOG(1-P0-P1) + LG1 - LG2 - LG3 + (ALPHA-1)*LOG(DV/SMAX) +
(BETA -1)*LOG(1-DV/SMAX)
IF(DV.EQ.0) LOGL = LOG(P0)
IF(DV.EQ.SMAX) LOGL = LOG(P1)
Y = -2 * LOGL
$ESTIMATION MAXEVAL=9999 METHOD=1 -2LOGLIK NUMERICAL LAPLACIAN
$COVARIANCE PRINT=E MATRIX=S
```

Results

Figure 1. Psoriasis Area Severity Index (PASI) scores over time (observed) and individual-level predictions (IPREDs). Left figure panel depicts subjects across dose groups in study 1311.1, right panel depicts dose groups in study 1311.2.

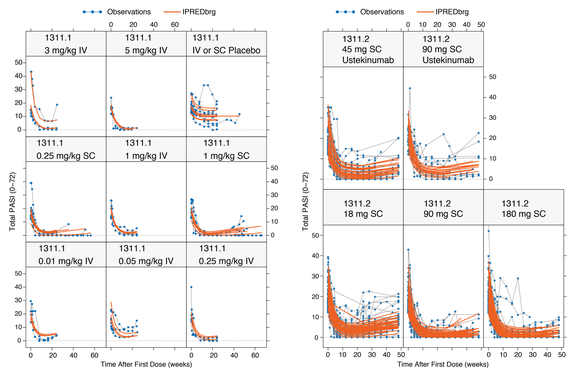

Table 2. Fixed and random effect parameters of the current BI 655066 PK-PD model of PASI data.

θ/ ω^2	Parameter	Units	EST	SE	RSE (%)	CV IIV (%)	Description
1	Baseline	(-)	-1.01	0.05	4.73		Rescaled PASI baseline-logit scale
2	kout	(-)	0.04	0.00	2.19		Fractional first-order rate constant
3	IC50	(ng/ml)	x	0.05	10.1		Concentration at 50% of maximum PASI inhibition
4	Imax	(-)	1.90	0.24	12.6		Maximal inhibition of PASI
5	Hill coef.	(-)	0.20	0.03	14.4		Power coefficient for the Emax relationship
6	tau	(-)	27.1	0.46	1.68		Beta reg. dispersion parameter
7	kPLB	(-)	0.47	0.10	22.1		Maximum placebo effect
8	gamma1	(-)	2.86	0.04	1.50		Augmented distribution param. 1
9	gamma0	(-)	1.69	0.05	2.69		Augmented distribution param. 2
10	Uste Offset	(-)	xx	0.21	11.3		Ustekinumab IC50 offset param
1	$\omega^2(1,1)$	(-)	0.19	0.02	12.42	43.2	Random effect baseline PASI

Figure 2. Change from Baseline PASI Visual Predictive Check. Orange points and black lines are observed PASI response and observed 5th, 50th and 95th percentiles of PASI across time for dose groups of 1311.2. 90% prediction intervals for the corresponding 5th, 50th and 95th intervals were constructed taking into account between-subject variability (blue polygons and green lines).

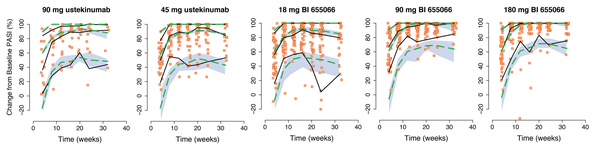

Figure 3. PASI 90 and 100 response rates Visual Predictive check using the current PASI PK-PD model. Black dashed line represents the observed PASI 90 or PASI 100 response rates. Polygons were constructed to include 90% of simulated response rates from 200 simulations of the original dataset, taking into account between-subject variability.

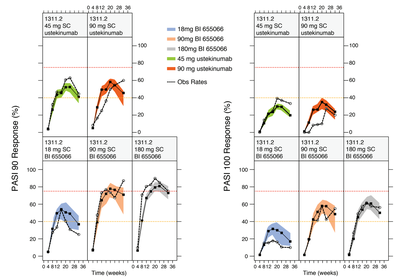

Table 3. Impact of bodyweight on PASI responses. Predictions of BI 655066 PASI 90 or PASI 100 response rates across time for a fixed dosing regimen, using the current PASI PK-PD model.

PASI 90				PASI 100			
Week	Body Weight (kg)	Median Response Rate (%)	5–95% Interval	Week	Body Weight (kg)	Median Response Rate (%)	5–95% Interval
12	60	69	(62–76)	12	60	47	(39–55)
12	90	68	(59–75)	12	90	46	(38–54)
12	120	67	(58–75)	12	120	44	(36–52)
16	60	77	(70–83)	16	60	56	(47–64)
16	90	75	(67–81)	16	90	53	(47–62)
16	120	72	(66–81)	16	120	52	(43–61)
24	60	82	(76–88)	24	60	63	(56–71)
24	90	80	(72–87)	24	90	61	(53–69)
24	120	79	(72–85)	24	120	60	(52–68)
28	60	80	(72–86)	28	60	61	(51–68)
28	90	78	(70–84)	28	90	58	(49–66)
28	120	76	(68–85)	28	120	55	(46–64)

Conclusions

- An augmented beta regression model for psoriasis data with responses at the boundary of the scale was developed and implemented. This approach reflects the reasonable expectation that conditions that make (non-zero) low-valued observations likely will also make zero-valued observations likely. Future methodological work could explore alternative mathematical formalizations of this general assumption.
- **Figures 1–3** illustrate goodness of fit of the current model with predictions of change from baseline PASI, and PASI 90 and PASI 100 response rates over time as diagnostics of key clinical interest. The current model reflects high potency (IC50) of BI 655066 in the picomolar range and a high degree of maximal fractional inhibition of the PASI formation process (kin) (**Table 2**). Various forms of the concentration–PASI Emax relationship are currently investigated.
- As with other IgG mAbs binding a soluble target, body size is a notable covariate of BI 655066 pharmacokinetics. Simulations of PASI response were undertaken to examine the functional impact of body weight on the efficacy (PD) of BI 655066 (**Table 3**).
- Typical subject simulations were undertaken for individuals weighing 60, 90 or 120 kg at key time points of interest under various dosing regimens for BI 655066.
- The lower weight individuals exhibited higher responses irrespective of the assessment time period on account of higher predicted exposure. PASI responses were predicted to vary by less than 5% across this wide range of prototypical body weights under consideration.
- Although based on an incomplete dose-ranging trial, this current analysis represents a key consideration in the definition of a regimen for future Phase 3 studies in psoriasis.

References

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