Markov modeling of side effect related dropout rates by introduction of previous state memory

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Background

- A possible side effect of niacin products is flushing, which is associated with cutaneous vasodilation (manifested as redness) of the face, neck and torso, and variably accompanied by a feeling of warmth, itching, and/or tingling.
- Tolerance to niacin-induced flushing develops when niacin is given repeatedly; however, this side effect may limit patient compliance until tolerance is achieved
- ASA is known to reduce flushing severity
- Two phase II studies (N=252, 6wks and N=241, 4wks) have been used in order to predict the dose response time profile for simultaneous dosing of Niaspan and ASA
- The model was challenged as it had to simulate dropouts of a 16 week study (N=384) see figure4
- Patients used an electronic device to record their daily flushing severity on a scale form 0 to 9 (daily records were not available for 16 week study)

Methods

- The model for the flushing severity was fitted using a cumulative logistic model in NONMEM. In order to do so, the response of the patients was classified in five categories: 0=no flushing, 1=mild flushing, 2=moderate flushing, 3= (very) severe flushing and 4=dropout due to flushing.
- Adjanced observations are correlated, thus a cumulative logistic model with markovian elements was investigated [1]. The introduction of markovian elements resulted in a objective function drop of 2,000. Thus the 12 additional parameters, needed for the markovian modeling, are justified. Thus the probability of being in one state depends on the previous state (figure 2,3).
- Introduction of a flushing memory, which accumulates the flushing severities of previous days (DADT(3) in NONMEM code), helped to further improve the model.
- The two studies were simulated 150 times using TrialSimulator. 90% prediction limits for patients with a certain flushing were obtained (figure 1)
- The mean transition rate for each simulation was calculated and compared to the mean observed transition rate (figure 2)

NONMEM code

```
$PROB Markov model for Niaspan related flushing and dropout
$INPUT ...
$DATA ...
$SUBROUTINE ADVAN6 TOL=6
$MODEL
 COMP=TOL
 COMP=CTOL
 COMP=FHST
$PK
 NIAF =     THETA(17)  ;concentration buildup rate
 KTOL = EXP(THETA(18)) ;tolerance buildup rate
 EFMX =     THETA(19)  ;Maximal drug Effect (EFF)
 AMAX =     THETA(20)  ;maximal ASA effect
 FBLD = EXP(THETA(21)) ;flushing history buildup rate
 HSTF =     THETA(22)  ;history factor for flushing memory
 M1   =     THETA(23)  ;Scaling factor, maximal tolerance
 M2   =     THETA(24)  ;Scaling factor, history influence
 AC50 =     THETA(25)  ;EC50 for ASA
$DES
 DADT(1)= NIAF*KTOL*(NIA/2000-A(1)) ; pseudo concentration model
 DADT(2)= KTOL*(A(1)-A(2))          ; Niaspan tolerance
 DADT(3)= FBLD*FPRV*(1-A(3))        ; flushing history/memory
$ERROR
 ;drug effect on flushing
 EFF = EFMX* A(1)*(1-A(2))*(1-AMAX*ASA/(ASA+AC50))*(1+A(3))+T26+ETA(1)
 ;history/memory effect on dropout
 DEFF= HSTF*A(3)
B1 =THETA(1)
 B2 =B1-THETA(2)
 B3 =B2-THETA(3)
 B4 =B3-THETA(4)
IF(FPRV.EQ.1) THEN
 B1= THETA(5)
 [...]
ENDIF
IF(FPRV.EQ.2) THEN
  [...]
[...]
ENDIF
IF(FPRV.EQ.3) THEN
 B1 =THETA(13)
 B2 =B1-THETA(14)
 B3 =B2-THETA(15)
 B4 =B3-THETA(16)
ENDIF
; Logits
 C1 =EXP(B1+EFF)
 C2 =EXP(B2+EFF)
 C3 =EXP(B3+EFF)
 C4 =EXP(B4+DEFF) ; !!! DEFF !!!
; Probabilities for Y>=0, Y>=1, etc...
 P1 =C1/(1+C1)
 P2 =C2/(1+C2)
 P3 =C3/(1+C3)
 P4 =C4/(1+C4)
; Probabilities for Y=0, Y=1, Y=2
 PA =1-P1
 PB =P1-P2
 PC =P2-P3
 PD =P3-P4
 PE =P4
; Select appropriate P(Y=m)
 Y=0
 IF(DV.EQ.0) Y=PA
 IF(DV.EQ.1) Y=PB
 IF(DV.EQ.2) Y=PC
 IF(DV.EQ.3) Y=PD
 IF(DV.EQ.4) Y=PE

$THETA ...
$OMEGA ...
$ESTIMATION LAPLACE MAX=9999 PRINT=1
METHOD=COND LIKE NOABORT
$COV
$TABLE ...
```

Results

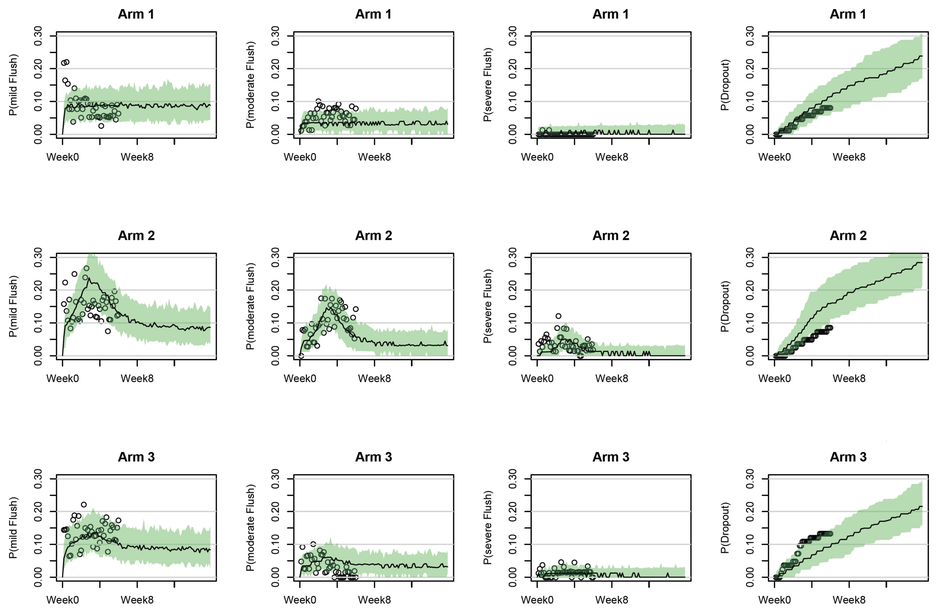

Figure 1: Visual predictive checks for one Phase II study arms (N=150 simulations/arm)

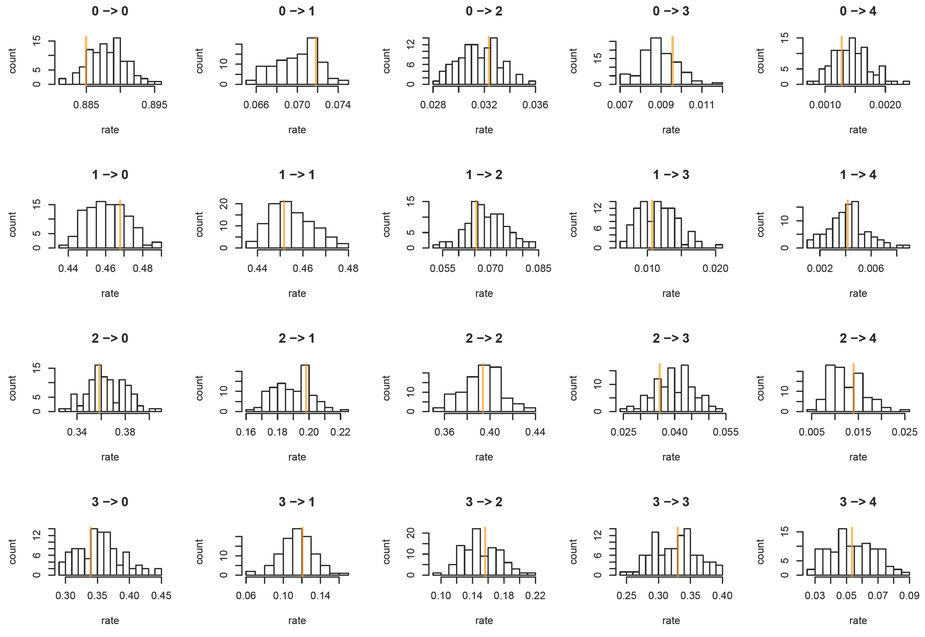

Figure 2: Visual predictive checks for the mean transition rate between flushing states (orange: mean observed rate for both phase II studies)

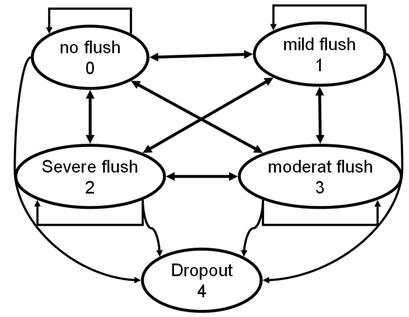

Figure 3: Illustration of the transit model

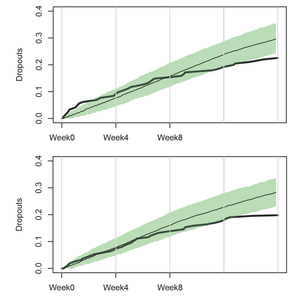

Figure 4: Dropout estimates for two arms of the 16 weeks study, which was not included in the modeling

Conclusions

- Visual predictive checks as well as dropout predictive check support the current model
  - Flushing scores can be appropriately modeled with the current model.
  - Dropout rates can be modeled as well, but the model should not be considered reliable proof for a dropout superiority study
- EC50 for ASA was estimated as ~234mg, thus a potential ASA dose to mitigate niacin related flushing is in the range of 250 to 350 mg

References

[1] Zingmark, P.-H., Kagedal, M., & Karlsson, M. (2005). Modelling a spontaneously reported side effect by use of a markov mixed-effects model. Journal of Pharmacokinetics and Pharmacodynamics, 32(2), 261-281.