

Fixed Dosing of Leuprolide Acetate, a GnRH Agonist, in Children with Central Precocious Puberty: A Population Pharmacokinetic Justification

Running heading: Fixed Dosing of Leuprolide in Children with Central Precocious Puberty

Pediatric Drugs

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SUPPLEMENTAL METHODS:

The study protocol was approved by the institutional review board for each study centre below and written informed consent/assent was obtained from each patient prior to enrolment.

List of Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs)	
Investigator Name	Name and Address of IEC/IRB
Jennifer Abuzzahab, MD	Institutional Review Board (IRB) of Children's Hospitals and Clinics of Minnesota 2525 Chicago Avenue South #61020 Minneapolis, MN 55404
Yaw Applagyei-Dankah, MD (site did not enroll subjects)	MUSC–Office of Research Integrity 171 Ashley Avenue PO Box 250857 Charleston, SC 29425
Clifford A. Bloch, MD	Western Institutional Review Board 3535 Seventh Avenue SW Olympia, WA 98502-5010
Carlos J. Bourdony-Baez, MD	Quorum Review IRB 1601 Fifth Avenue, Suite 1000 Seattle, WA 98101
Mario I. Brakin, MD	Quorum Review IRB 1601 Fifth Avenue, Suite 1000 Seattle, WA 98101
Kenneth Copeland, MD	Institutional Review Board–OU Health Sciences Center 100 Stanton L. Young L1B176 Oklahoma City, OK 73106
Mark Danney, MD (site did not enroll subjects)	Quorum Review IRB 1601 Fifth Avenue, Suite 1000 Seattle, WA 98101
Erica Eugster, MD	Indiana University IRB Union Building 618 620 Union Drive Indianapolis, IN 46202
Patricia Fechner, MD	Children's Hospital and Regional Medical Center Institutional Review Board 1100 Olive Way, Suite 500 Seattle, WA 98101
Sherry L. Franklin, MD (site did not enroll subjects)	Quorum Review IRB 1601 Fifth Avenue, Suite 1000 Seattle, WA 98101
Mitchell Geffner, MD	Children's Hospital Los Angeles Committee On Clinical investigations (CCI) 4650 Sunset Boulevard MS#23 Los Angeles, CA 90027

Luis Gonzalez-Mendoza, MD (site did not enroll subjects)	Western Institutional Review Board 3535 Seventh Avenue SW Olympia, WA 98502
Carol Huseman, MD	Children's Mercy Pediatric Institutional Review Board 2401 Gillham Road Kansas City, MO 64108
Lydia Irizarry-Gonzalez, MD	Quorum Review IRB 1601 Fifth Avenue, Suite 1000 Seattle, WA 98101
David H. Jelley, MD	Oklahoma Health Science Center Institutional Review Board 1000 Stanton L. Young Boulevard L1B176 Oklahoma City, OK 73117
Karen Klein, MD	University of California, San Diego Human Research Protection Program 9500 Gilman Drive, MC 0052 San Diego, CA 92093
Gad Kletter, MD	Western Institutional Review Board 3535 Seventh Avenue SW Olympia, WA 98502
Mark Kummer, MD	Nemours Florida Institutional Review 10140 Centurion Parkway North Jacksonville, FL 32256
Kashif Latif, MD (site did not enroll subjects)	Quorum Review 1601 Fifth Avenue, Suite 1000 Seattle, WA 98101
Peter Allen Lee, MD, PhD	Human Subjects Protection Office, A115 Penn State Milton S. Hershey Medical Center Penn State College of Medicine 600 Counterview Drive, PO Box 855
Nelly Mauras, MD	Baptist Medical Center Institutional Review Committee 800 Prudential Drive Jacksonville, FL 32207
Kenneth L. McCormick, MD	Western Institutional Review Board 3535 Seventh Avenue SW Olympia, WA 98502-5010
Robert McVie, MD	Louisiana State University Health Sciences Center-Shreveport Institutional Review Board (IRB) for the Protection of Human Subjects #2 Office of Sponsored Programs and Technology Transfer 2627

Bradley S. Miller, MD, PhD	Research Subjects' Protection Programs, University of Minnesota Mayo Mail Code 820 420 Delaware Street SE
Edward Kirk Neely, MD	Admin. Panel on Human Services in Medical Research Administrative Panel Office Stanford University 1215 Welch Road, Modular A
Francisco Nieves-Rivera, MD	Western Institutional Review Board 3535 Seventh Avenue SW Olympia, WA 98502-5010
Fermin A. Sanchez-Lugo, MD	Quorum Review IRB 1601 Fifth Avenue, Suite 1000 Seattle, WA 98101
Lawrence Silverman, MD (site did not enroll subjects)	Atlantic Health IRB PO Box 1905 Morristown, NJ 07962-1905
Janet Silverstein, MD (site did not enroll subjects)	Western Institutional Review Board 3535 Seventh Avenue SW Olympia, WA 98502-5010

NONMEM control stream of the final model:

\$INPUT C STDY ID AMT CMT DV MDV EVID ...

\$DATA ".../.../..."

\$SUBROUTINE ADVAN13 TOL=8

\$MODEL NCOMP=3

COMP=(DEPOT1,DEFDOSE) COMP=(DEPOT2) COMP=(CENTRAL,DEFDOBS)

\$PK

IF(NEWIND.NE.2) THEN

DOST=0

DOSP=0

DAMT=0

ENDIF

IF(EVID.EQ.1) THEN

DOSP=DOST ;previous dose time

DOST=TIME ;current dose time

DAMT=AMT ;dose amount

ENDIF

F2=0

FRAC=THETA(1)

FABS=THETA(2)

F1=FABS*FRAC

BIO=FABS*(1-FRAC)

;lag time for first process

ALAG1 = THETA(3)*EXP(ETA(3))

;lag time for second process

ALAG2 = THETA(4)*EXP(ETA(4))

KA1 = (THETA(5))*EXP(ETA(5))

KA2 = (THETA(6))*EXP(ETA(6))

TVCL=THETA(7)

CL=TVCL*EXP(ETA(1))

TVV2=THETA(8)

V2=TVV2*EXP(ETA(2))

S3=V2

TVN=THETA(9) ;number of transit cmt

N=TVN

TVMTT=THETA(10) ;mean transit time

MTT=TVMTT*EXP(ETA(7))

K13 = KA1

K23 = KA2

K30 = CL/V2

KTR=(N+1)/MTT

LNFAC=LOG(SQRT(2*3.141593)) + (N+0.5)*LOG(N) - N

\$DES

X=1E-10

IF(T.GT.DOST) THEN

TD=T-DOST

ELSE

TD=T-DOSP

ENDIF

DADT(1) = -K13*A(1)

DADT(2) = EXP(LOG(BIO*DAMT+X)+LOG(KTR+X)+N*LOG(KTR*TD+X)-KTR*TD-
LNFAC) - K23*A(2)

DADT(3) = K13*A(1) + K23*A(2) - K30*A(3)

\$ERROR

IPRED=F

Y=F+F*ERR(1)+ERR(2)

\$THETA (0,0.9,1) ;FRAC

\$THETA (1 FIX) ;FABS

\$THETA (0 FIX) ;ALAG1

\$THETA (0 FIX) ;ALAG2

\$THETA (0,0.4) ;KA1

\$THETA (0,0.01) ;KA2

\$THETA (0,200) ;CL

\$THETA (0,10) ;V2

```
$THETA (3 FIX) ;N  
$THETA (0,50) ;MTT
```

```
$OMEGA BLOCK(2)  
0.1 ;IIV_CL  
0.05 0.1 ;IIV_V2
```

```
$OMEGA 0 FIX ;IIV_ALAG1  
$OMEGA 0 FIX ;IIV_ALAG2  
$OMEGA 0.1 ;IIV_KA1  
$OMEGA 0.1 ;IIV_KA2  
$OMEGA 0.2 ;IIV_MTT
```

```
$SIGMA 0.1 ;PROP  
$SIGMA 0 FIX ;ADD
```

```
$EST METHOD=1 INTERACTION MAXEVAL=9999 PRINT=5 NOABORT POSTHOC  
$COV MATRIX=S
```

```
$TABLE ID TIME DV MDV EVID IPRED CWRES ONEHEADER NOPRINT
```