Hi

clinical pharmacology program

Today were going to be doing a followupactivity to Joe Rogaborus [spelled phonetically] PKPD modeling and well be performing anactivity to demonstrate how to build a PKPD model and explore the different ways thatthese models can be used for clinical drug development and to gain a better understandingof the pharmacology of whatever drug youre studying

So a PKPD model is essentially an exposureresponsemodel describing the relation of the drug in terms of how much drug molecules are circulatingthrough your body and how thats tied to whatever response that youre looking at

So all drugs have a desired effect on targetthat theyre designed to hit and also some side effects off target effects

And while the desired effects are studiedobviously we want to also study the offtarget effects because if the drug is too toxicthen patients cant tolerate it and then they go offstudy and they dont get the benefitof the drug

So during clinical drug development phaseones two and three a toxicity profile is generally developed and identified and alsoresponse models

So we can gain a better understanding ofexposureresponse relationships with these drugs throughout the clinical developmentand then we can use that data to build said models

The drug in question that well be discussingtoday is called beleodaq; the generic name is belinostat

It is a secondgeneration histone deacetylaseinhibitor

It is because it is a second generationit has all the HDAC inhibitors in this generation have a hydroximate molality onthe end of their molecule and that makes

it a good handle so to speak on the drugmetabolism for glucuronidation and well cover that shortly here

It was FDAapproved in 0 for peripheralTcell lymphoma relapse to refractory at a dose of 000 milligrams per meter squaredas a 0minute IV infusion

Its pharmacokinetic profile is best describedby a rapid distribution into the periphery and rapid elimination with a short halfliferanging from 0 to three and a half hours in humans in plasma

And like other drugs in its class hydroximatehistone deacetylase inhibitors it is predominately glucuronidated by the polymorphic UGTA

And there are two particular sites where thegene UGTA is altered

One is the genotype where theres anextra region in the promoter that reduces its expression hence reduces its activity

And patients with the one or two copieshave a slower metabolism and slower clearance

So they have overexposure of drug

And then same with UGTA0 different sitesame effect

So we built a PKPD model that describesthe genotype effects along with every other kind of population characteristic that weincluded

And this will also tie into Dr Beezus [spelledphonetically] population PK lecture where he described how to build a population PKmodel which is what this is

And we noticed here that patients that werecarriers of the andor 0 had a slower rate of metabolism

And during this infusion which was a hourinfusion this is a different study and a different disease setting so in this casethe study was trying to get the drug approved in a different disease setting to ad on tothe FDA approval of peripheral Tcell lymphoma

And so because it has a short halflifethis study had a prolonged hour infusion to prolong the drugs effect

And during the drug infusion the black linehere represents the steady state of drugs exposure for impaired metabolizers

And as you can see its higher than peoplewith regular or extensive metabolism

So this sort of proves our hypothesis thatpatients with these genotypes do have a slower metabolism and a higher exposure

And the model did simulate a slower clearancefor the impaired metabolizers

In the lower left figure there the red boxdepicts a clearance for the impaired metabolizers and it has a slower clearance rate than extensivemetabolizers

And so in order to not overdoes impairedmetabolizers we simulate a dose reduction that when you do the does reduction in impairedmetabolizers you get a more comparable exposure

So you are helping those patients not havetoo much toxicity

So the purpose of this activity is to gothrough the steps to build a PKPD model

So what were going to do first is now thatweve described the PK model were going to go through the process of putting thatmodel together in terms of text so that we can understand how that PK model is built

So the pharmacokinetics is essentially justdescribing the kinetics of the drug over time

So in order to do that we use differentialequations and were describing the movement of the drug from the central compartment inthe plasma to the periphery and then back into the central compartment where it canbe metabolized and cleared

So the top two lines there are the differentialequations of describing the drug movement in the first or second compartment as wellas a variety of other lines of code that we will get to

So this overall line of code here describeseverything that we would need for the Pop PK model

The first section highlighted in red hereis the structural model

So this is where you can code a twocompartmentmodel structure and also describing the rates

into and out of each compartment

We have four parameters that the model isestimating; the volume of each compartment one and two the clearance rates intoand out of between the compartments and then the overall systemic clearance rate outof the body

And so we have a variety of ways that wecan do that

So the type of model this is is a mixedeffectpopulation model

So the mixedeffects is a mix of the fixedand random effects

And one other aspect to a structural modelhere is the unexplained error

So we try to explain as much error in themodel as possible and the unexplained portion of error we can still describe by a proportionalmodel which is highlighted here in yellow

The fixedeffects is represented by the populationaverage of that parameter

So for instance lets say one of these parametersis body weight for an easy example

So if everyone in the world a populationweighed themselves youd have a population average

Lets call it 0 kilograms

Some people weigh more some people weighless

Trying to understand the reasons why certainindividuals weigh more or weigh less you would have a population average weight andthen other covariates to explain why said individual might weigh more or less than thepopulation average

Are they taller?

Are they older?

Are they younger?

What is their diet?

Et cetera

So in the parameter equation to calculateeach individuals parameter estimate you have a population average for that parameterand then other covariates or variables that

help describe why that patient might havea slightly different value for that parameter than the population average

So again the fixed effects are just thepopulation average

Then we have the random effects which arethose portions of the equation for each parameter that help describe why one patient has a differentvalue for that parameter than other patients

And as we all know not everyone reacts tothe drug the same and theres a variety of reasons why that is

It could be organ function age sex genderrace a variety of things

So in this study we noticed that in additionto the base level between subject variability represented by the EDA [spelled phonetically]values we have a bunch of covariates

And we built a covariate model on top of ourbase structural model and in this particular drug in this particular study with the studydata that we had available such as albumin and renal function and obviously the UGTAgenotype status those were the variables that significantly impacted the clearance

And the volume of the central compartmentbody weight did explain some of the variability on that parameter

So that is the population PK aspect of thisPKPD model

So now we want to talk about the PD aspectof this PKPD model

And first were going to do two parts to thePKOD analysis

First were going to do the ontarget desiredeffects which the HDAQ inhibitors inhibit histone deacetylases

And in histones there is a regulated functionof relaxation and tightening of chromosomes around histones the DNA around histones

So and thats regulated by histone acetylationtransferases and histone deacetylases

And so the histone acetylases inhibitorsinhibit the deacetylation

So knowing the mechanism of the drug is importantto develop this PKPD model

So with that said we know that belinostatand other like drugs histone deacetylase inhibitors inhibit deacetylase activity atcertain histones on certain lysines

So what we ultimately can measure as an indirectmarker of drug effect is global lysine acetylation

Its an easy validated way to assess thereduction of the activity of the enzyme without actually measuring the enzymes activity directly

So we indirectly measure just global lysineacetylation

And as the drug works and inhibits deacetylationacetylation levels go up

And thats how we can mark drug effect

So building on top of our PK model wereadding a PD response model where knowing that our measured response is global lysineacetylation we have a regulation of the acetylation by acetylation and deacetylation in termsof the model its modeled by

A Kin and a Kout rate respectively

The drug effect for belinostat is on the deacetylationaspect or the Kout because belinostat inhibits deacetylation enzymes

So and we can mark we can track ourresponse over time with the differential equation listed here

And because its a reversible mechanismthe effect the inhibitory effect IMAX and IC0 are tied into the drug concentration

So when the drug concentrations zero theeffect will be zero

And that captures the reversible aspect ofthe mechanism

So with the diagram of the model depictedhere lets next go through how to actually build that model in a in an analysis software

So we need the differential equations textuallyto build that model

The PK model code here is the same as we justdiscussed in red so we dont need to cover that again

But the PD aspect of the model here is inblue

And as we can see if we want to track thechange in response over time or the change in effect over time so we have the fourparameters here that we need to estimate for the model

The PD model is the Kin and the Kout ratesthe IMAX and the IC0

So the time component of this effect modelis tied indirectly to the drug concentration which in itself is tracked by time

Drug concentration changes over time as adrug is eliminated and the drug concentration magnitude will change with dose

So those all can be tied into the effect

So after we can implement this code intoour whatever software were using and

a side note: This model code here is in thePhoenix modeling language but it can easily be deciphered into NONMEMFortran or MATLABor any other comparable PK modeling software

The essence is the same; youre having a differentialequation to describe the drug effect or drug concentration over time and the nature ofthat differential equation doesnt change

Some syntax might change but the essenceof the code depicted here will apply almost in every software

So once we implement that code into our softwareand implement the data set that has all the data variables that we need we can simulatewhat a exposureresponse PKPD relationship would look like

And in this diagram here the blue lines arerepresented representing the drug concentration for this study which was a hour infusion

So as drug levels increase up to a steadystate during the infusion you can also see a correlated increase in the global acetylationfold change indicated by the red line

And on the right axis the right Y axis thereis the global lysine fold change acetylation

And as the drug infusion is stopped at hours and the drug is quickly cleared due to the quick halflife of the belinostatthe global acetylation levels quickly fall

back to onefold which is baseline

So this model can adequately capture thereversible mechanism between belinostat drug concentrations and the histone deacetylaseinhibition

So while that was the relationship with thedesired effect we also have to understand the offtarget undesirable adverse effects

And in this case many of the drugs in thisclass including panobinostat romidepsin and belinostat all have links to thrombocytopeniawhich is a decrease in platelets

The mechanism of this drug effect on plateletsis a delated maturation of the platelet precursor which is a megakaryocyte and if the drugcan delay the maturation of the precursor into the mature thrombocyte then youre eventuallygoing to deplete your thrombocyte your mature thrombocyte count over time especially withrepeated cycles of drug and its going to take your body longer to recuperate and replenishyour mature thrombocyte levels

So with repeated dosing of panobinostatromidepsin and belinostat eventually patients have grade two or grade three or worse thrombocytopeniawhich can be resolved with platelet infusions but its still a it can be a doselimitingtoxicity for a time which will require the patient to dosereduce or delay a dose butthen theyre just not getting the desired effect that they need

So we need to understand this relationshipa little bit better

Its been published for panobinostat and severalother drugs in this class but never for belinostat

And that is something that was recently publishedby our group

So as I said this effect on this drug classhas been published before

So what we can do is take whats been publishedinto literature in terms of a PD response model for megakaryocyte maturation and drugeffect on it and apply that to our study here

So we have our same PK twocompartment modelhere where the drug concentration is now linked to a drug effect in the yellow boxthere where it delays the maturation of the megakaryocytes

And so this is a semimechanistic representationof a drug effect on thrombocytes

And the code for this the PK aspect againis the same in red and the PD aspect here is in blue

And well go through each section of codeone by one describing this figure here

So there are several aspects to this figurethat the code will represent

So the first section is understanding theproliferating compartment

And we have a differential equation here tomeasure the amount of proliferator cells or megakaryocytes based on the rate going tomake them and the rate going to mature them

And thats where the drug effect is

And our drug effect which is described bythe caption there E drug is actually a linear effect on the effect with concentration

So we have a slope parameter that were measuringthat is tied to the drug concentration

So the drug concentration is linearly relatedto the drug effect

And that relationship is described by theslope parameter

The next section is the maturation sectionwhere the megakaryocytes are sequentially matured in these transit compartments andthese transit compartments can be described with differential equations as depicted here

And then the last section here is the circulatingcompartment of mature thrombocytes or mature platelets which is what we are measuringclinically

Were measuring when we take samples frompatients were measuring their circulating platelet count

And this is where we can use this observedata to build our model around and to and to estimate each of the parameters that weneed to estimate in this model code

And so what we can do is build a model estimateour parameters it gives us the predicted number of circulating platelets and we cancompare that to our observed or measured amount of platelets and see how far off we are

And that will help us to optimize our parameterestimates and come up with the best model

And weve done that and with our optimalmodel with our optimal parameter estimates

which are listed here below in the fixedeffects there then we can simulate a PKPD

response in terms of platelets

So the left Y axis is again depicting thedrug concentrations during a hour infusion

And you see as you increase dose from 0in green to 00 mgs per meter squared in red

obviously your steadystate concentrationincreases accordingly and correspondingly

so does the delayed rebound effect of theplatelets

So on the lowest dose there in green onthe right Y axis is a circulating platelet

count measure

And as you can see the green line kind ofrebounds the fastest which makes sense; you

have the lowest concentration of drug

And the highest concentration of drug thehighest dose of drug you actually rebound

the slowest and you dont actually fullyrecover by the end of the day cycle

So by the start of the next cycle on day you arent really at the highest does

level at least in this simulation

Youre not fully rebounded yet

So any subsequent doses your NADR [spelledphonetically] is just going to go lower and

lower and eventually that dose is going tocause in most people a at least grade two

thrombocyte count thrombocytopenia event

So what this model is useful for is if youknow someone is a UGT variant and theyre

going to clear the drug slower even withthe same dose as everybody else they may

have a higher exposure

And we can correlate their higher exposurewith how slowly theyre going to rebound in

their platelet count

So you can try to predict when and how severetheir thrombocytopenia event will occur and

you can try to back down their dose earlyenough to avoid this situation

And that reduction in dose can be optimizedby simulations

Personalized

So that is all I have

I hope this activity was helpful for you andthank you for your time