we are fortunate to have dr yanning wang

dr wang is currently the acting director

and the deputy director in the division

of pharmacometrics in the office of

clinical pharmacology at the fda

before joining the fda dr wang received

his phd in pharmaceutics and masters

degree in statistics from the university

of florida

he also obtained a masters degree in

biochemistry and a bachelors degree in

pharmacy from peking university in china

at his current position dr wang oversees

review research projects and policy

development within the division of

pharmacometrics please enjoy todays

lecture

hello everyone my name is janing wong

im the acting director and deputy

director of division of pharmacometrics

under the office of clinical

pharmacology at fda

today i will talk about a very

interesting and important topic during

the drug development

though selection and optimization in the

adult population

ill start with a brief overview

followed by the organizational alignment

of different therapeutic areas within

fda for new drug review and approval

typically i use

real examples to make my point in my

talk therefore i will spend most of time

talking about case studies

initially i planned

to include one case for each therapeutic

area to demonstrate the unique feature

of drug development or drug dose

selection for different therapeutic

areas but given the time minute i

eventually cut it down to 0 cases but

thats still a lot of information so

lets get started

as we all know those selection or

optimization is done throughout the

entire drug development process

in the preclinical setting

in vitro system or

animal studies were conducted to

investigate the pharmacology toxicology

and sometimes effective concentration

and to figure out the safe starting dose

for human subjects

and in the clinical phase those

optimization of selection is a

continuous process

in phase one the primary focus is the

exploration of acute toxicity and

tolerability

and then in most

in most

disease areas phase two studies will

explore several doses or dosing regimens

to identify the dose or doses to be

studied in phase three

in most programs phase three studies

only include one dose level but in some

programs as you see later

can include more than one two or three

doses to further

optimize those in the last few years we

have seen an increasing number of post

marketing studies designed to further

optimize those even after the drug is

approved

the obvious motivation for those

optimization is to balance the risk

benefits at the population level or at

the subgroup level or even at individual

level to achieve the ultimate

precision medicine or individualized

medicine

in addition to the risk benefit balance

convenience and marketing

competitiveness are also important

factors for those selection or

optimization

these are the six offices currently at

fda that include totally different

divisions of therapeutic areas

as you can see

for example office of antimicrobial

products or oep

includes division of antieffective

products dvd of antiviral products

division of transplants and

ophthalmology products then the other

office office

and office of hematology and oncology

products include the rest of the

therapeutic areas

in the next few slides in the next

one hour or so i will go over

0 case studies

not only to demonstrate

how the dose was selected during the

drug development but also to show you

some very important clinical trial

design features such as which

therapeutic area will use superiority

design and which therapeutic areas will

use noninferiority trial design

and the clinic endpoints and even sample

size typically used at a different

stages of drug development

now i hope this talk can also serve as a

reservoir of

case studies for most therapeutic areas

and

of course there are many more excellent

examples or case studies the reason i

picked the following 0 cases is because

i was involved in most of the cases and

im quite familiar with them

so lets get started case one

double vancing well

please excuse me if i cannot pronounce

some drug names correctly because some

of them are quite

tongue twisters

this drug is from the division of

effective products it was proved in

0

and is indicated for acute bacterial

skin and skin structure infections

caused by designated susceptible strains

of gram positive micrograms

the recommended dose is one thousand

milligram on day one followed one week

later by 00 milligrams

the dose selection

for this case represents the typical

dose selection process for

antieffective products and this is one

of the few disease areas where the pre

the preclinical applications drug

concentration can be directly translated

to the

clinical education concentration

mainly because the interaction between

the drug and bacteria is relatively

independent of the infected species and

of course their exceptions do

so in this case as we can see the

individual tests and in vivo animal

studies

identified that the area under the

plasma concentration curve over minimal

inhibitory concentration or auc over mic

as the most relevant exposure metric to

evaluate the efficacy

in addition the minimal

bacteriocyte concentration or mbc or

specifically the concentrations produce

at least a three log ten reduction in

titer in the time kill experiments were

also quantified

also the in vitro study identified that

the less frequent and larger dose is

more effective than more frequent and

smaller doses

so based on these

preclinical studies

you may know there is a typical

safety driven dose selection for the

first in human dose selection

then the phase one doses were selected

as you can see there is a single

ascending dose that studied that those

range from 0 to 00 milligrams and

this is also a multiple ascending dose

or mad study that covered 0 to 00

milligrams over seven days and up to

00 milligram over eight weeks

typically phase one study is intended to

identify the socalled maximum tolerated

dose within healthy volunteers but these

studies dont have to push the dose

as high as possible until you reach the

mtd in fact in some cases the sponsor or

the company will set up maximum dose

which is believed to be well above the

efficacious concentration identified

from the preclinical studies and they

can stop there too even though thats

still not the maximum target dose

so in this case there were two

phase two clinical studies

one is in the skin and soft tissue

infection and the other is in catheter

related blood stream infection

the first infection investigated two

different dosing regimens

one is the single dose of 00 milligram

and the other is a two dosing regimen

with one thousand milligram on day one

followed by 00 milligram on day eight

and the comparator is active control

as you can see in this area placebo

control trial is not allowed for obvious

ethical reason

so between these two different dosing

regimens the two dose regimen

or the

weekly dosing regimen achieve the

highest response rate

compared to the lower dose

and the active competitor

in addition a daily dose such as 0

milligram on day one followed by

milligram daily for two weeks was also

studied but given the excellent efficacy

of this

weekly regimen

and the convenience of only

administering two doses the daily

regimen was stopped and therefore this

once every week regimen was continued

into the phase three trials and studied

in two independent phase three trials

against the active control to

demonstrate

the noninferiority

against the active control

this plot shows the plasma concentration

under this once weekly dosing regimen

during a day period

as we can see the first dose was given

at day one and the second dose was given

seven days later

and the top solid line represents the

total plasma concentration

and the bottom dash line represents the

free drug concentration and the

horizontal dash line represents the mbc

level identified from the preclinical

setting

as you can see even the free

concentration is well above nbc

throughout the most of the period of

days

and therefore this regimen was studied

in phase trials and was shown to be

similar to the act control and

eventually was approved

case two is for

symmetrophore and this is from the

division of antiviral products

it was approved in 0 and indicated

for the treatment of adults which with

hp hcv infection

the proved dosing regimen was 0

milligram qd once a day

plus pagolated interferon alpha and

ribovarium for weeks

followed by or additional weeks of

pagolated interferon

plus ribovarin depending on the prior

response status and the presence of

hiv coinfection

similar to the

antieffective case

extensive preclinical studies were

conducted to explore the effective

antiviral concentration in various in

vitro systems and the safe concentration

in various animal species in order to

determine the safe dose first first in

human dose study in addition viral

mutation and resistance to the drug was

studied extensively in the in vitro

system across various viral genotypes

fist one study were also conducted in

healthy volunteers to identify the

maximum tolerance dose

through

single ascending dose or multiple

ascending dose studies

for this program even a limited number

of hcv patients were also including the

phase one study to explore the efficacy

so given the time limit i will focus on

the phase and phase studies from a

dose selection perspective

multiple dosedraining phase studies

were conducted phase a and phase b

the range of doses in this phase a

study were based on the effective

antiviral concentration estimated from

the in virtual systems

the pharmacokinetics and safety data

from phase studies and even the labor

distribution of the drug in animal

studies

a short period of placebo monotherapy is

allowed in this disease area then the

different doses were added to the to a

background of active treatment

demonstrate better efficacy or added

value of the new drug

based on the results of this phase a

study the lowest dose study was found to

be less efficacious than higher doses

and the highest dose studied 00

milligrams showed increased bilirubin

for both treatment naive and experienced

patients

therefore the next dose ranging phase b

studies included milligram and 0

for treatment naive patients and a 00

milligram and 0 milligram qd for the

treatment experience patients

in addition to the two different dose

levels

different

treatment durations were also optimized

in fact this is the unique feature of

this case studies we dont have many

examples that study or optimize the

treatment duration and this is one of

the examples

the control arm was placebo plus active

regimen

and the results of this study showed the

0 milligrams the higher dose in both

naive and experienced patients

showed better efficacy and there was no

additional benefit beyond weeks of

treatment

and therefore this regimen that is 0

milligram qd plus the active control

which is pagolate interferon and

ribavarian for weeks versus the

placebo plus pr

was studied to show the new regimen is

superior to the competitor although this

trial is a superiority trial design

so here is the trial design for the

phase b

study that was

targeting the treatment experience

patients

as we can see in addition to the two

dose levels

three different treatment durations were

compared weeks weeks and weeks

and the control arm is placebo plus pr

as you can see the shortest duration arm

is for weeks then the remaining

weeks will be using the placebo plus pr

so that all the treatment will have

equal length of weeks of treatment

then efficacy will be based on the

primary efficacy endpoint svr which

stands for sustained biologic

response at 0 weeks

later 0 weeks after the planned end of

treatment which is the weeks that is

weeks after the weeks so the

results of this studies demonstrate that

the there was no obvious difference in

terms of efficacy between the three

treatment durations but the higher those

demonstrate better efficacy and

therefore this regimen was further

studied in the phase three trial

and it was proved in the end

the third case is aeronautics this

product is from the division of

transplant products it was approved in

00

i have to say i have a long history with

this drug

when i joined fd in 00 this early

summation just came in for the early

indication as you can see the drug was

approved after long journey multiple

rounds of submissions and two advisory

committee meetings

i was lucky enough in the 00 period to

review the early submission for the

kidney indication and the hard

indication which was not approved in the

end

then about 0 years later

i

somehow magically got involved in the

labor indication of

review and it was proved in 0

anyway

so the proved indication include both

kidney and labor transplant and the dose

approved for kidney transplantation was

starting oral dose of 0 milligram

twice daily as soon as possible after

transplantation

in combination with vasalix map

cyclosporine with reduced dose and

corticosteroids

for liver transplantation the approved

dose was starting oral dose of one

milligram twice daily starting 0 days

after transplantation in combination

with tachoratamus with reduced doses and

corticosteroids

for both indications therapeutic

monitoring or tdm was required in order

to adjust the maintenance dose to

achieve a target concentration of

three to eight nanogram per ml target

range using a lcmsm ac method

this is actually one of the few examples

that studied

drug concentration level during the drug

development

and i learned a lot through the 0 years

similar doses were studied

the selection of aeronautics dose for

clinical studies was initially based on

individual and individual primate data

for efficacy

further selection of the two doses of

aeronautics which is 0 milligram and

milligram bid tested in the phase

were based on the safety tolerability

and pharmacokinetic results from kidney

transplantation studies

in addition the anticipated aeronautics

drug exposures were similar to the

exposures reported for the seronamus

which had the same maximum action in

pivotal trials in renal transplantation

in fact the company initially did not

apply tdm to the new drug anonymous

instead they conducted two phase three

studies comparing two fixed doses of

aeronautics 0 milligram and

milligram bid plus standard exposure

cyclosporine and corticosteroids to the

active control arm

microphenolate

morphetel one gram bid plus standard

exposure cyclonic and carticle steroids

the goal was to show noninferiority or

similar efficacy for renal

transplantation

the results did show similar efficacy

but worse renal toxicity mainly because

of the interaction between aerodynamics

and the renal toxic drug cytosol

similar doses were studied in one heart

transplantation trial

since the comparator was not the optimal

regimen the goal was to show superiority

on efficacy

again the efficacy goal was achieved but

the safety was not acceptable

the company did extensive exposure

efficacy and safety analysis to figure

out the optimal concentration windows

for both aeronautics and sites flooring

to minimize the renal toxicity without

compromising effects

at the same time fda reviewers also did

similar analysis to help the company

identify the optimal therapeutic windows

for both drugs

the results supported mg nanogram per

ml as the lower limit of efficacy as a

lower limit of aerodynamics for efficacy

and nanogram per ml as upper limit

since little incremental benefit was

observed at exposures above 9 nanogram

per ml

also given the exposure dependent renal

toxicity the exposure of the background

cycle throwing level was reduced to

minimize the renal toxicity

then the company was asked

to conduct a prospective clinical trials

to evaluate the therapeutic drug

monitoring therapy

this is the trial design for the tdm

based regimens with reduced dose of

background cycle throwing group one

is the lowdose

plus the low

therapeutic window

for the average

and group two is the high dose plus a

high therapeutic window for aeronautics

both doses were combined

with the lower therapeutic monitoring

window for the cyclists fluorine

compared to group that has the

standard cyclosporine therapeutic window

as you can see the cyclosporine

concentration

was dramatically reduced compared to the

standard arm especially during later

months

this is the observed concentrations

of aeronautics on the left side

and cyclosporine

on the right side

and the horizontal lines represent the

planned therapeutic window limits

and the

box plots represent the actual observed

concentrations for both everyone

elements and size flooring

with this new therapeutic drug

monitoring strategy the low starting

dose

with the target of to nanogram per

ml and the reduced sex flowing levels

achieved similar efficacy and similar

renal toxicity compared to the control

arm

and the higher dose still had worse

renal toxicity

therefore

the low dose plus the low target window

regimen was eventually proved for kidney

transplantation

a similar tdm based trial was conducted

for the hard indication

unfortunately the high dose with high

concentration window was terminated

prematurely due to higher mortality

in fact even the low dose with the low

concentration window

also showed a higher mortality rate at

month in a subgroup compared to the

control arm

in addition the renal toxicity was worse

for the lowdose control lowdose

algorithms group compared to the control

arm

the company contributed this worse renal

function to noncompliance of patients

with the reduced cyclosporine level

nevertheless the heart indication was

not approved by the fda and if you want

to understand the possible reasons for

the increased mortality you can read the

reference paper at the bottom of the

slide

a slightly different design was used

for the heart for the labor indication

the control arm was the standard dose

tachronolimus as demonstrated

with the control with the standard dose

tachrolimus

and heres the

therapeutic window

for less than three months or later than

three months for the tachrons

concentration

there are two new regimens one is

reduced tachronomas plus average and the

other is called eliminated tachromes

plus aeronautics

tachoramus is well known for its renal

toxicity therefore the goal of these two

new regimens was to minimize the

background tacrolimus in order to

improve the renal toxicity

as we can see in the reduced tachromes

arm

the target concentration of tachomas was

significantly reduced compared to the

control arm

at the same time a to nanogram per

ml of aeronautics was added to maintain

efficacy

and the third arm was a more aggressive

arm

as you can see after three months the

goal was to

totally eliminate attack chronologists

by adding more aerodynamics

at a higher level between six and ten

unfortunately the third arm did not work

out mainly because right after three

months there was a significant increase

of events including

acute rejection deaths and or

graft loss

suggesting that

adding more aerodynamics while removing

all the tacrolimus was not able to

maintain the efficacy

therefore the focus became the

comparison between the control and the

reduced acronyms arm

as you can see

theres there are several new features

for this design that is there was a

onemonth delay between the

transplantation and the randomization

and this onemonth gap was added to

avoid or minimize the known toxicity

from aeronautics

specifically wood healing complication

edema and thrombosis

but this one months also led to a

significant loss of patients as you can

see

about 0 of patients did not make it to

the randomization or only 0 of patients

were remaining for randomization

in other words this remaining subsets

almost represent an enriched

subset of original transplant patients

and this trial was designed

as a noninferiority trial

so the most difficult part of this trial

actually turned out to be the

calculation of noninfer not only for

early march

as we all know historically we calculate

noninferior margin based on historical

trials similar to the current trial

but because of the special feature

no historical trial could be identified

to represent this enriched subset

as a result there were many rounds of

discussion between fda and the company

in terms of how to derive this

noninferior margin

and there was no good answer and in the

end sponsor went ahead and did this

trial using a noninferior margin of

but after the trial was finished since

there was no agreement on this

noninferior margin

we could not evaluate the efficacy

during the review cycle so the review

team was stuck

in the end a novel approach using

exposure response analysis and we were

able to derive a new noninferior margin

based on the current data

and that new noninferior margin plus

additional

efficacy data from other indications and

from maximum action were used eventually

to prove this product

so i wont have the time to go into

details of this method if youre

interested you can read the second

reference on the slide to understand how

it was done

the fourth case is edoxaban this is from

the division of cardiovascular product

it was proved in 0 it has two

indications the first indication is to

reduce the risk of stroke and synthetic

systemic embolism

and the recommended dose is 0 milligram

once daily in patients with creatine in

clearance between 0 to 9 milliliters

per minute

and for patients with creatinine

clearance greater than 9 milliliters

per minute the drug should not be used

and for patients with creatine clearance

between and 0 milliliter

preliminates the dose should be reduced

to 0 milligram

the drug also has a second indication

with the

recommended dose but for this

case i will focus on the dose selection

for the first indication

the phase three dose regimen was

selected

based on the integrated knowledge from

the earlier phases

phase one pk or pharmacokinetic

pharmacodynamic and drug drug

interaction study

suggested those reduction for patients

or for subjects with renal impairments

impairment concomitant use of pgp

inhibitors or low body weight

and phase two studies in subjects

undergoing low extremity or therapeutic

surgeries and subjects with atrial

fibrillation showed that the bid regimen

led to higher bleeding rates than qd

regimen and the sixth milligram qd

showed better efficacy compared to 0

milligram qt

in addition exposure response modeling

assimilation showed that the both the 0

and milligram bid dosing regimens

resulted in plasma concentrations that

remained above the seeming at steady

state corresponding to the warfarin

bleeding rate while the 0 and 0 qt

dosing regimens had concentrations

elevated at this level for approximately

and 0 hours respectively

based on the concentration based on all

this information it was concluded that

0 milligram qd can be considered the

best tolerated higher dose regimen

compared with warfarin which is the

active control in the phase trial and

the 0 milligram dose was included to

evaluate two regimens in a large phase

three trial in order to maximize the

chance of finding the optimal regimens

of edoxaban compared to warframe from

both safety and efficacy perspectives

again this was a noninferior comparison

for efficacy

and endocrine dose reduction by 0 were

recommended for moderate renal

impairment patients can common use of

specific pgp inhibitors and low body

weight patients

this plot shows the efficacy assessment

based on the drugs effect on intrinsic

factor

0 activity

under the milligram qd regimen the

steady state concentration level was

sufficient to achieve a peak inhibition

of ninety percent of baseline activity

within one two three hours after dosing

in addition the trough values were

consistent with the seventy percent

media inhibition

therefore it was believed that this

regimen should provide adequate

inhibitory activity through the whole

day based on this biomarker endpoint

this plot shows the bleeding events

observed in the phase doseranging

study

given the same in the same daily dose

such as 0 milligram dose

the more frequent dose 0 milligram bid

led to a higher bleeding event rate than

the six million acuity

and here the warframe eventuate and

heres another

higher even higher dose six milligram

bid

based on the results of this phase two

study qd regimen was carried on to the

next phase

during the review fda reviewers found

that the control of inr in the warfarin

arm was suboptimal in this

dosedraining study as demonstrated by

the large percentage of

patients with inr less than two during

the trial

this finding led to the conclusion that

the dose finding study resulted doses

that were too low

and this can also explain the major

review issue which is

phase results suggested inferior

efficacy relative to warfarin in the

normal renal function subgroup for both

doses

on ischemic stroke

and this was the major issue for the

advisory committee meeting discussion

this slide shows the relative risk of

ischemic stroke or since systemic

embolism events between the induction

arm and the warfarin arm based on the

renal function subgroups

the right table

shows the absolute event rate per

patient here

and the red numbers

and the symbols

are for the higher those and the blue

numbers and the symbols are for the

lower doses

and the key problem is for the subgroup

with normal renal function at the bottom

of the slide

as you can see for both low and high

doses

the relative risk

between edoxaban and warfarin is above

one suggesting induction is worse than

warfarin in terms of preventing

ischemic stroke and se

and for the other two groups only the

higher dose

demonstrated either better or comparable

efficacy relative to warfarin

the lack of efficacy in the subgroup

with normal renal function was linked to

the lower drug exposure

this slide is only shown in the result

of the high dose again by renal function

subgroups

efficacy on the left

drug exposure or pk in the middle

safety or major bleeding on the right

so for the subgroup with the highest

exposure which is the mild

with which is a subgroup with mild renal

function

the exposure is highest

efficacy was the best and the bleeding

risk was highest closest to warframe in

contrast the subgroup with normal renal

function had the lowest drug exposure

and correspondingly worst efficacy

and almost

and the best bleeding risk

so

as a result

and in fact this kind of concentration

explorer dependent

efficacy and safety relationships were

observed across multiple compounds in

this disease areas

as a result only the high dose was

approved for this indication in certain

subgroups defined by the renal function

and a significant portion of patients

with normal renal function could not use

this drug because of the inferior

efficacy compared to warfarin

the fifth case is fingolimod

this is from the division of neurology

it was approved in 00 and is indicated

for the treatment of patients with

relapsing forms of multiple sclerosis

the recommended dose is 0 milligrams

already once daily with or without food

the product label

also has a detailed list for first drug

monitoring based on several

cardiovascular safety endpoints

specifically pulse rate blood pressure

and ecg so this drug has some safety

issue

the success of this product is closely

related to the dose fingolimas

mechanical action

is to sequester lymphocytes in lymph

nodes preventing them from contributing

to autoimmune reaction

and this compound was derived from

immunosuppressive natural products

with certain chemical modifications

reduced original toxicity

and single mod was first developed for

the prevention of acute rejection after

renal transplantation

in adult de novo renal transplant

patients at a daily dose of 0

milligram and 0 milligram in

combination with cyclosporine and

corticosteroids but it was discontinued

due to too much toxicity

later a sixmonth phase ii clinical

studies in multiple sclerosis showed

efficacy of fingolamod mri matters as

well as relapse endpoints with a lower

dose and the milligram dose but

with no difference in efficacy between

the two doses

then the phase phase trials

included even lower those 0 and

and demonstrated better efficacy

compared to both placebo or the and the

active control

but there was no difference in terms of

efficacy between these two doses

this drug was proved as the first oral

drug to treat multiple sclerosis with a

postmarketing commitment study to

explore a lower dose of 0 due to its

dosedependent toxicities

this slide shows the dose response for

both efficacy on the left

and safety on the right

within the studied dose range a very

flat dose efficacy relationship was

observed while a positive dose safety

relationship was identified for multiple

safety endpoints

in order to explore the efficacy of a

lower dose

a serious models were used to link those

to drug exposure

and then to biomarker response

and then finally to the clinic endpoints

in order to predict the efficacy of the

lower dose

this linked model was used to directly

link the drug concentration to the final

clinical endpoint ar annual annualized

relapse rate

and this is the predicted ar rate for

the lower dose

in comparison with the higher dose and

the placebo and active control

in other words we believe that even

lower dose such as 0

could achieve similar efficacy at a

higher dose with the potential of

improving the safety profile

and this analysis was presented at the

advisory meeting and

served as the basis for the

postmarketing commitment study to

further optimize the dose for this drug

the next case is polyperadol

palmitate extenders release injectable

suspension

and this drug was from the psychiatric

product and it was proved in 00

and its indicated for the treatment of

schizophrenia

and this table includes the recommended

dose

and i added and the dose we include

initiation dosing at day and day and

followed by monthly maintenance dose

i added a series of

another those levels beside all this

dose level

just to facilitate the connection

between these those levels and the

numbers you use in the next few slides

and during our review

the original doses levels were expressed

in terms of

equivalent dose

for example the 0

milligram dose in the table is

equivalent to the 0 milligram in the

next few slides

and the major conversion factor is the

molecular weight difference between

polyperadine and this thought form

and ill explain why this was done in

this case

in the next slide

what we were reviewing this injectable

suspension

the extend release tablet

was already proved as a qd regimen

and the active product ingredient for

the tablet is peripheral and thats why

the dose of this new

injection formulation was initially

expressed as paraparative equivalent

dose

and the doses studied in the clinical

trials are listed here

and the one trial studied multiple doses

without loading those and another study

explored the loading dose plus different

levels of maintenance dose

but in the end

the sponsor proposed an entirely

different dosing regimen that was not

directly studying any one of the phase

three trials

that is with a 0 loading those at day

one that another relatively high loading

dose 00 milligram on day eight

followed by milligram as the monthly

maintenance dosing regimen

then you may ask why would the sponsor

propose a new regimen that was not

directly studied in any one of the phase

trial

we will show the results of this loading

those results loading

those studies here you can see on the

yaxis is the change from baseline in

pen score which is the affix endpoint

for this trial

and

with relative to placebo all the active

arms showed better efficacy

but in this trial one death was observed

at 0 milligram dose and there was also

those dependent increase in body weight

and ethereum prolactin levels

to improve the risk benefit ratio the

sponsor

did not pick any one of these doses

instead they picked as the monthly

maintenance

so to roughly estimate the efficacy of

this new regimen we can imagine

it should be between these two

horizontal lines because the second dose

is still 00 but the third dose started

milligram

so then you may ask why not 0

milligram

so this light

should provide additional support

for the milligram

as as i said earlier the qd regimen

was already proved it had been on the

market for quite a while

the blue shaded area represents the safe

and effective concentration window under

the qd regimen

therefore under the monthly regiment

the steady state concentration

represented by the red line will fall

within this

shaded area

thats the additional rationale for the

sponsor to propose this milligram

dose as the maintenance monthly dose

as you can see this is the case that

demonstrated the final proof dose

doesnt have to be

the study dose in the clinical trials

it can be a new regimen derived to

achieve the best risk benefit profile

based on the phase retards

the second case is dopa glyphosate

this is from the division of metabolism

products it was proved in 0 after two

runs of advisory committee meetings

and is indicated as a junk to diet and

exercise to improve glycemic control in

adults with type diabetes

and the recommended dose is to start

with final acuity and then those can be

increased to 0 minute acuity if the

patients can tolerate the drug and also

require additional glycemic control

this drug has an extensive clinical

pharmacology program including many

clinical trials related to those

again phase one study includes sad

mad and also a phase a doseranging

trial

and a dedicated lowdose pkbd study to

study a wider and lower dose range

and many drug drug interaction studies

special specific population studies

to derive the dose that can potentially

be used under these special conditions

and there was also exposure response

analysis to quantify the relationship

between exposure and response and all

these are related to those optimization

these are all the late phase clinical

trials

three phase to be those ranging trials

were conducted

one as a monotherapy

one as addon therapy to insulin and one

dedicated study in japanese population

as monotherapy

even in all these three three phase

three trials you will see that most

trials included two or even three dose

levels either as a monotherapy

or addon therapy to various background

therapies

this slide shows the wide range of doses

divided for the effect on hour

glucose excretion in the urine

given the maximum action of this drug

even healthy subject could provide

efficacy evidence which is the blue line

and the blue symbols

and the red curve and red symbols are

for the patients

in general a e max model can describe

the dose response relationship very well

and the vertical line at 0 milligram

was the target those the company was

trying to develop

this is the phase two study that helped

the dose selection for the phase three

program

five dose levels ranging from

milligrams to 0 milligram was studied

against placebo in treating naive

patients with type diabetes

after weeks of treatment

our doses achieved better efficacy than

placebo

the company selected and 0

milligrams for further development

because the clinical meaning for

incremental reduction of hpc which is

efficacy endpoints was not observed in

doses greater than 0 milligrams

so this slide

compared to other cases this case has

the most extensive dose selection

program

even in all these phase trials as you

can see either as

monotherapy at the bottom or combination

therapy

either two or three doses were studied

as demonstrated in this column

relative to different comparators either

placebo or act control or addon therapy

and the trial duration was weeks or

longer

this slide summarizes the efficacy

across all phase trials both

milligram and 0 milligrams showed

better efficacy than the comparator

while the 0 milligrams showed a

numerically better efficacy than

milligram

as a result the final proofed regimen is

to start with milligram and increase

to 0 milligram

if patients can tolerate the dose and

need additional glucose control

strictly speaking this type of titration

regimen was not directly studied in any

one of these phase trials

but it was considered the best dosing

regimen to balance the risk benefits

given the totality of evidence

so this is another case that

demonstrated the flexibility of fda

to accept a derived

regimen with better risk benefits based

on the finished phase three trials

so the eight case is indicator

it is from the division of pulmonary

products it was proved in 0

and the maximum action is called

longacting beta agonist

a class of a drug called lava

the indication is for chronic

obstructive pulmonary disease or copd

in fact the drug was not approved during

the first cycle the company got a

complete response later in 009 and the

main issue was those of course it was

finally proved but interesting part is

us proved the dose of microgram qd

while the other countries proved higher

doses 0 and 00

and i will see why

before we go to the

details of this drug we need to

understand the risk for this whole class

of drug called laba

multiple advisory meetings discussed the

risk of this class of drug

and this new england journal of medicine

article summarized the findings from

those meetings

specifically a metaanalysis based on

0 randomized parallel controlled

trials of the use of lava for asthma

patients

demonstrated a higher risk for laba

compounds in terms of the risk of

asthmarelated deaths

incubation or hospitalization

and this risk should be kept in mind

while we are going through the rest of

the

cases

again relative to most oscar cases this

one also has a relatively

extensive dose selection program

this table lists the key placebo

controlled clinical studies

including several studies related to

those or those in regimen

the three studies in the white box

were conducted after the first cycle or

after the cr ladder was issued

and the study bs

was the pivotal dozer indian study

during the first cycle

that included those range from to 00

microgram qd

com in comparison with placebo or active

control

and there are additional phase trials

either during the first cycle or during

the second cycle

so lets first look at the first dozen

indian trial during the first cycle this

trial was designed as adaptive seamless

trial

to pick the dose for the next phase

two doses was selected

after

five doses were evaded for two weeks

and in comparison with placebo or active

control

so well see in the next slide what

criteria were used to select these two

doses

two prespecified

efficacy criteria were

used to select the two doses moving to

the next phase

the first criteria was

day fe

should be above this horizontal line

and the second criteria was

d

fev

between one and four hour auc

should be above this horizontal line

after applying these two fx criteria

0

and 00

microdose were selected to continue with

the longterm treatment

as you can see

these two horizontal lines were defined

as

minimal

clinical effective

effect compared to the placebo

according to the company

this is a slide that was intended to

show the lack of tachyphylaxis over

weeks

but i

i want to highlight another interesting

observation

that is a more obvious dose response

was observed at the early time points

among 0 and 00

while the that dose response

relationship disappeared over time

suggesting even the lower dose such as

microgram could be as good as a

higher dose over time

or

putting another way a lower dose needs a

longer time to reach its maximum effect

while a higher dose can achieve its

maximum effect relatively fast

thats why in

other trials that compared to 00 of 0

there was no difference in efficacy

between these two doses

in the long run

so here are the reasons for the complete

response ladder during the first cycle

you can find in our review

the submitted data did not provide

substantial evidence of safety to

support the use of this drug at the

proposed doses of 0 and 00 once daily

in patients with copd

at the proposed doses there were

unacceptable higher frequency of serious

adverse events compared to placebo or

active control either in place either in

copd patients or asthma patients

and this is again tied back to the

known risk of lava compound because this

drug also blends water

the submitted studies did not

show a clinical meaning for efficacy

difference between the micrograms

once daily compared to the higher doses

or between 0 and 00

and a proper dosing frequency has not

been explored in clinical studies

and the submitted data did not provide

substantial evidence to support use of

the two different doses in patients with

copd

the data submitted did not show a

clinical meaningful advantage of the

higher dose over the loadouts especially

given the potential safety of the higher

dose again from this class of drug

then the company did additional

doseranging studies to explore even

lower doses

this one was conducted in copd patients

for two weeks

the lowest dose went down to

microgram

once a day

again comparing between day and day

a very obvious pattern is at day you

see a very clear dose response

suggesting higher dose had a better

efficacy than the lower dose but at day

that advantage almost disappeared

entirely

then the company

did another study with the same dose

ranging in asthma patients

in fact the typical dose draining study

for cop indication is conducted in

asthma patients because it was believed

asthma patients are more sensitive to

differentiate different doses

and similarly

when you compare the day and day

the dose response relationship is much

more obvious at day compared to day

in addition to those two doseranging

studies focusing on qd regimen

the company also conducted a dedicated

study to explore the impact of dosing

frequency on efficacy

the results show that given the same

total daily total dose

more frequent such as

bid

or less frequent such as once every

other day

are similar to the qd regimen in terms

of efficacy

therefore all the following programs

were focusing on the qd regimen of

microgram

this is the last slide for this case

study

additionally additional week efficacy

studies were conducted for the micron

qd

and this slide shows a crosstrial

comparison of the key efficacy endpoints

fev improvement over placebo

between the microgram and the higher

dose 0 and the act control

and

given the

risk benefit of this whole class of lava

fda in the end only improved the

microgram and even published the

rationale in a new england journal

medicine article and i put the reference

on the first slide of this case if you

want to know the details you can look at

the paper

the nice case is

plastics for

this is from the division of hematology

it was proved in 00

and indicated to enhance mobilization of

cd cells to the preflow blood for

collection and subsequent or to log

autologous bone marrow transplantation

in patients with nonhodgkins lymphoma

and multiple

myeloma the initially proved dose was

0 milligram per kilo based on the

actual body weight

later the dose was updated to a new

regimen and the main change is for

patients with body weight less or equal

than kilo

either a fixed dose of

0 milligram dose or the original

milligram per kilo dose can be used

and this case represents the scenario

where a postmarketing study can further

optimize those to improve the risk

benefit profile for subgroup

during the review of original submission

we identified a subgroup with

suboptimum efficacy as shown in this

table

based on the primary efficacy endpoints

which is mobilization of million cd

cell per kilo within four days

in the long hard lymphoma patients

the placebo corrected

response rate was only percent for

the patients with weight less than

kilo

while it was for the heavier

patients

even though the new regimen was already

better than placebo in both subgroups we

believe there was

still room for improvement for the

lighter patients

our analysis showed that the low drug

exposure in the lighter

patients under the milligram per kilo

dose may be the reason for the sub

optimal efficacy results

in this figure that left plot shows the

auc of the new drug across different

body weights

under the milligram per kilo dose

and the middle plot as you can see all

the patients with low body weight

their exposure was lower than the

heavier heavier patients

the middle plot

shows the predicted aoc or area under

the curve if a fixed dose of 0

milligrams was given to the lighter

patients

and the

right plot shows the predict aoc if one

third of those reduction was applied

to all patients with renal function or

renal creatine clearance less than 0mg

per ml

the goal of this dose adjustment was to

achieve similar drug exposure across the

whole bodyweight range

we predicted that the higher exposure

in the lighter patients under the fixed

dose

0 milligram big

fixed dose should improve efficacy in

that subgroup

so in our review we conclude that the

currently proposed body weight based

dose results in a lower exposure in

patients with low body weight compared

to patients with higher body weight

and this decreased exposure was

associated with significantly decreased

efficacy in patients with low body

weight and the applicant or the company

agrees to design conduct and submit a

clinical study to optimize dosing in non

hodgkins lymphoma patients by matching

the exposure in the low body weight

people to the high body weight patients

so after the company finished the phase

study and submitted the results

we updated the product label and changed

those for lighter patients because of

the following three reasons

the fixed 0 milligram dose showed

fold higher exposure than the milligram

per kilo dose as

as we predicted

as a result of the higher exposure

the efficacy also improved for this

subgroup as demonstrated by a higher

response rate either by five percent

based on the local lab data or based

on the central lab data

in addition safety profile was also

similar between the two groups

therefore based on this postmarketing

study the dose

was

modified in the product label

resulting in a better risk benefit for

the lighter patients

heres the last case actually the last

case is a failed program

the compound name is ruslitanip

this is from the division of oncology

the program was terminated in 0 after

a dramatic story related to those

the proposed indication was for the

treatment of patients with mutants

epidermal growth factor receptor or egfr

nonsmall cell lung cancer who have been

previously treated with egfr targeted

therapy and have the egfr t90m mutation

as detected by fda approved test

this case was discussed last year at an

advisory committee meeting thats where

all the information is on the public

domain

this table

lists the regulatory milestone for this

compound

late 0 the clinical program started

then in may of 0

orphan drug designation was given to the

company because theyre dealing with a

very small population

in may of 0 a breakthrough

designation was offered to the company

based on an objective response rate of

then in july of 0

end of a meeting was held between the

company and fda

then next year in june

a preendeave was held and quickly a

rolling submission of nd initiated

raised the request from the sponsor for

excited approval

then in november 0

during the midcycle fd decided to take

this case to the advisory committee for

oncology which is called odac

then in december of 0 a major

amendment was submitted by the company

and therefore the purdue for goal date

the date was supposed to make decision

was extended to

june of 0

then we had our late cycle meeting in

march of 0

then advisory meeting in april of 0

to explain the requirement for

accelerated approval i need to show this

slide

so there are certain requirements in

order to give excited approval

first the condition of the disease

should be serious and lifethreatening

which is okay for this case

and second is a very important one the

treatment under

review should provide improvement over

available therapy which means the new

regimen should have better efficacy or

potentially better efficacy than

available therapy

and third studies should use the

surrogates reasonably likely to predict

clinic endpoint which in this case

objective response rate

and in the end we will need a

confirmative trial postmarketing trial

to confirm the benefits by using the

clinical endpoints

this is how the dose issue evolved over

time in july 0

0 the company proposed 00 milligram

bid as the dose

but then in january 0 the dose was

changed to milligram bid because the

cumulative data suggested a numerically

higher objective response rate for this

dose

but in february 0

fdes review of pharmacokinetic data did

not support the milligram dose

then in march of 0

tiger which it was the ongoing phase

trial or the conformity trial to confirm

efficacy and initially only included 0

00 milligram and control arm

was amended by the company to add a

third arm 00 to

milligram because the company felt

this dose should have a better efficacy

however

fdas review of pharmacokinetic data

showed that despite the increase of dose

the drug concentration did not increase

both

cmax on the left

and area under the curve on the right

at the steady state

showed a flat relationship

with the doses ranging from high 00 to

000 milligram

and the reason is the poor solubility

and that led to this nonlinear form of

kinetic observation

so based on this pk finding fda pulled

the efficacy from three doses

studied and also more importantly

applied the correct definition of

objective response rate

then the updated orr became 0

as demonstrated here

instead of the original

when the breakthrough designation was

offered

this significant change of orr raised a

serious concern on the accelerated

approval pathway

because

another compound

rc mertinip

was already proved for the exact same

indication with a much higher

or rate of 9 percent

even though this compound was

also approved under accelerated approval

this means that ruslitanip

may not meet the requirement of better

efficacy than available therapy

in addition

fdas exposure efficacy analysis showed

a relatively flat relationship

suggesting the maximum efficacy could

have been already reached for this new

compound and no more additional benefits

could be achieved even with a higher

exposure

at the same time a very steep exposure

safety relationship was observed

for one toxic metabolite of this

compound

m0

higher the exposure

of the metabolites the higher rate of

grade or hyperglycemia

another toxic metabolite

m0

was found to be associated with qtc

plungation

under the proposed therapeutic exposure

the average qtcf plungation was about

milliseconds

worse than all approved oncology

products on the market

given this risk benefit profile

the voting results of advisory meeting

was to against approval of this

compound under the accelerated approval

pathway and shortly after the advisor

meeting the company terminated the

program

so thats the last example

so with the 0 case studies

i hope you can see that

those selection or optimization is

integrated in the entire drug

development process

different disease areas have different

risk benefit rationales to justify those

in regiments

some disease areas have more extensive

dose selection programs than other

disease areas but in general

those optimization is becoming more and

more important

especially in the era of precision

medicine

finally id like to thank all my

colleagues

in the division of pharmacometrics

office of clinical pharmacology office

of biostatistics and office of new drugs

for the collaboration over the years

review to review all these excellent

cases

i also would like to thank all the

sponsors we call the drug companies the

sponsors for the drug products

they tried their best to identify the

best dosing regimen within the limited

resource and time and sometimes

proposed innovative methods to derive a

better regimen than what was studied in

clinical trials and their efforts should

be appreciated as well

thank you for viewing the courses if you

have any questions please contact course

coordinator thank you very much

you