Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Isavuconazonium sulfate		
Name of Active Ingredient: Isavuconazole		

SYNOPSIS

Title of Study: A Phase 1, Open-Label, Multicenter, Non-comparative Pharmacokinetics and Safety Study of [redacted]

[redacted]

Pl (c lnnbNr SHl tuA ezf u re daoj e d ynh a A tota l of 0 pediatric ub ect were enrolled in 2 s s the age cohort , en uring there would be at lea t 8 ub ect evaluable for the primary ana ly i in each cohort. s s

C s s D l o ac dr tar mM o g ia The lu i y u po pulation con i ted of ub ects who, in the opinions s s s of the treating phy ician, could benefit from i avuconazonium ulfate in the prophylactic etting. Th e e s included tho e at high ri k for inva ive fungal di ea e, uch as children with hematological malignancy including SCT recipient . s

s , c s t r Ae to D d o ,s eu d o Tl d m :M rd t ns f o t aB nb Nr na Co mmercialii avuconazonium ulfate s for in ection, batch number 9 994 . 2 2

(D r t o ro t n, tel r D o a t n c o i S) y n d f b u n The ma imum period of do ing wa to be s 8 day . 2 s

c , c r s e e r e A e to f D d o ,s e m R d o a d m :M rd t ns f o t aB nb Nr na There iva no reference product. s

l E : r t v r e o t a f o a au i i n i

E c c y No formal pro pectively defined efficacy a e ment were planned in thi tudy ss ss ca e of s s I breakthrough fungal infection, the ite of infection, cau ative organi m, start to p date , and any follow-up s s s information available regarding re olution and therapie u ed to treat the infection wa recorded. s

c cs r m d t a The pharmacokinetic endpoint i were a follow s s s

C_{max} , AUC$_{tau}$, t_{max} day and day 7 (iv only)
C_{trough} day and 7, and if applicable, day 4, s , 8 (iv only) s 1 21 2
Model-derived parameter CL, , AUC , t ss s ss 1 2

A preliminary pediatric population pharmacokinetic model wa developed ba ed on i avuconazole pla ma s s concentration data obtained from 8 ub ect irre pective of age cohort who received intravenou do e of s i avuconazonium ulfate, with 4-hour pharmacokinetic profile from 2 both day and day 7. Thi model wa u ed to e timate pharmacokinetic parameter to determine if any modification to the intravenou do ing regimen wa warranted. Enrollment wa not interrupted during the preliminary modeling. After all ub ect in Part had completed the tudy, all ub ect with at lea t one i avuconazole pla ma concentration were included s in the development of the final intravenou pediatric population pharmacokinetic model. The 4-hour s pharmacokinetic profile included blood ample collected on day (day), 7 (s day), and at the day 8 or 1 EOT vi it (or within day prior to the la t do e). f the 2 ub ect wa able to provide pharmacokinetic ample beyond day 7, trough ampling wa performed weekly (s day), appro imately 4 hour after prior day 2 s infu ion (i.e., within 5 minute prior to start of ne t infu ion) through day 8 or EOT. s 2

s c : S t t t a o Ob ed Mod pla ma concentration data for i avuconazole were li ted. ndividuals ub ect s I concentration-time profile (linear and emi-log cale), a well a overlay (paghetti plot) for each day by age s s cohort were produced. For the analy i of pharmacokinetic , de criptive tati tic included number of ub ect s s s (n), mean, SD, C , geometric mean, geometric C , median, minimum and ma imum. For the t_{max} , only n, median, minimum and ma imum wa calculated. s

Pharmacokinetic parameter (C_{max} , AUC$_{tau}$, and t_{max}) were li ted and ummarized u ing de criptive tati tic by s s age cohort and overall. A pediatric population pharmacokinetic model wa developed with intravenou data s ba ed on the already e tabli hed adult population pharmacokinetic model whereby model-derived s pharmacokinetic parameter (CL, , AUC and t ss) were e timated. 1 2 s

[redacted]

l C l / s Ssmm ry s s t ae of uo u R n n i

: ot A total of 9 ub ect were enrolled in thi tudy, and enrolled ub ect were not given tudy s s drug. Twenty- even ub ect were given at lea t one do e of tudy drug (con tituting the afety analy i et s s SAF). Of the SAF, 6 ub ect provided at lea t one valid pharmacokinetic mea urement (con tituting the s s pharmacokinetic analy i et P AS), and 4 ub ect completed the tudy Table 2 s. s s 1

The demographic characteri tic of the ub ect are de cribed in Table . The ubject were predominately s s male (ub ect , 7) and white (8 ub ect , 6), with age ranging from to 7 year . s 1 1 s

The primary underlying diagno e of the ub ect are hown in Table s . Acute myelogenou leukemia wa the s mo t common diagno i (0 ub ect , 7), followed by neuroblastoma (4 ub ect , 4.8) and apla tic anemia s s 1 (ub ect , .). s s 11 1

All (9 9) ub ect in Cohort and all but (6 8) ub ect in Cohort were 40 kg in weight and were do ed at 0 mg kg all (0 0) ub ect in Cohort weighed more than 40 kg and were do ed at 7 mg. s 2

Æ c c l c yc sr ms ffa ct a a t ei k u i i R

Efficacy No breakthrough infection were ob erved. s s

Pharmacokinetic A ummary of C_{trough} value on day and 7 are hown in Table 4 . A ummary of pla ma s pharmacokinetic parameter of i avuconazole after multiple do ing i pre ented by age group and day in s s Table 5 . Within each age cohort, there wa a tendency for C_{ma} and AUC_{tau} value to be lightly higher at day s s than at day 7. The median t_{ma} wa imilar acro all age group . When comparing acro age cohort , on day ss the mean AUC_{tau} and C_{ma} were comparable for Cohort and and were appro imately 0 to 5 2 lower for Cohort . On day 7 the mean AUC_{tau} and C_{ma} decrea ed a age increa ed. s s s

A population pharmacokinetic model wa developed from Part of Study 9766-CL-0046 for the intravenou admini tration of i avuconazonium ulfate. Due to limited number of pharmacokinetic ample , the data from s s Study 9766-CL-0046 were combined with that of 6 ub ect from Part of Study 9766-CL-00 8 who were 2 admini tered a ingle do e of 7 mg of i avuconazonium ulfate (iv), including 8 adult ub ect with varying s degree of renal impairment and 8 adult healthy ub ect . s s

Ba ed on modeling and imulation re ult , the propo ed daily do e for the clinical tudy in pediatric patient i s

0 mg kg i avuconazonium ulfate for patient weighing 7 kg (the ma imum loading and daily maintenance do e to be admini tered to any patient are 7 mg), s 2

O R

7 mg i avuconazonium ulfate for patient weighing 7 kg. s s

Detail of the modeling and imulation procedure and re ult are available in a eparate population s pharmacokinetic modeling report.

Ba ed on noncompartmental analy i of parameter on day and day 7, Cohort appear to have lower C_{ma} s and AUC a compared to Cohort and , however the e parameter might not be at teady state. Pla ma s s concentration data from thi tudy will be u ed to upport a population pharmacokinetic model developed for i avuconazole and for pharmacokinetic pharmacodynamic modeling. The re ult and the model development s s will be de cribed in detail in the population pharmacokinetic report i ued eparately from thi CS . ss s s

: s s S ty e t aEvfnt fromuEOT vi it thRt occurred on cheduled vi it dsays were di played under s s s
Day 8 EOT rather than the cheduled vi it day. s s

An overview of TEAE i hown in Table 6 . The TEAE occurring at the fre uency of at lea t 0 of s
ub ect (i.e.,) at the PT level in any inglestreatment cohort i hown in Table 7 . The TEAE with the
highe t fre uencie were pyre ia (5 .9), mucoal inflammation (44.4), diarrhea (s .), thrombocytopenia,
anemia, abdominal pain, epi ta i and pain in e tremity (. each). Only ub ect in Cohort 2 e perienced s s
AE in the SOC of n ury, poi oning and procedural complication . Otherwi e, there were no obviou s s
difference between the age group . s s

TEAE in 7 of ub ect (0 7) were con idered at lea t po ibly related to tudy drug Table 8 . The drug- s
related TEAE occurring mo t fre uently were infu ion related reaction, procedural nau ea, and procedural s
vomiting, each reported for (.) ub ect in Cohort . n the 2 cohort , no TEAE wa 1 een in more s s
than ub ect. Study drug-related TEAE were low in all cohort . s s

Overall, 44.4 (7) of ub ect e perienced an SAE. Overall, the mo t fre uent SAE were diarrhea and s s
pyre ia (. ub ect each), followed by febrile neutropenia, abdominal pain, muco al inflammation, and s
cytomegalovirus infection (7.4 ub ect each). The number of SAE for individual event wa very low. s s

Only SAE (electrocardiogram T prolonged) wa con idered at lea t po ibly related to tudy drug. This s s
SAE re ulted in di continuation of tudy drug on day 8. s s

AE re ulting in di continuation were reported for ubject Table 9 . 2 s s

n thi tudy, multiple intravenou doe of is avuconazole were generally afe and well tolerated by male and s
female ub ect in all age cohort , with a afety profile which wa imilar to adult . s s s

UO O NS S N L I

Thi wa the fir t tudy in which the afety and pharmacokinetic of i avuconazonium ulfate wa s s
formally inve tigated in children. s
On day , C_{max} and AUC_{tau} were comparable for Cohort and , but were lower for Cohort 1. On 2
day 7, AUC_{tau} and C_{max} decrea ed with increa ing age. A population pharmacokinetic model wa
developed to determine appropriate do ing regimen in children. s
avuconazonium ulfate wa generally afe and well-tolerated in thi tudy, with an overall AE s s
fre uency that wa imilar to what wa ob erved in adults. The fre uency and type of AE observed
wa e pected ba ed on the underlying medical condition of the tudy population. s s
No obviou difference in overall and individual-type AE wa ob erved between the age cohort s s
Study drug wa withdrawn in ub ect due to liver to icity, and in 1 ub ect due to T prolongation. 1 s
Two ub ect e perienced mild event but tudy drug wa not withdrawn by the principal s
inve tigator. s

: D t oe rt ae 7 Dec 0 9 **p R** 1 2 1

[redacted]

b c sles A Sb Pt D esk Tu s o jy d ast p rein ni i n a i 1

ss	y CSt æ nC 6 6s = ( ) ( )	i r6 o t y r s e t a oy< = ( ) ( )	rto o l (n 1) (n)	h rto o s(t a oy< 1 n) (n) n	h t o e 1a <1 n 1 n	h a n n
s	t r e e d R gi	(00)	8 (00)	11 1 0(00)	1 9(00)	1 1
sss	S ty y at f a a n	9(8 .8)	8 (00)	1 0(00)	1 7(9 .)	1 1
l c c	r m s s d a y t a k	n 9(8 .8)	i 8 (00)	19(90.0)	1 6 (89.7)	
sc	r t m t e e t a d t o T a u n n (i 8.) i	i (.5)	2 1 2(0.0)	1 125 (7.)	2 2	
s v	v r d e t e e e	n 0	(.5)	(0.0)	1 12 (6.9)	1 1
l	s t c r b y b a t a e u i h	(9.)	0	1 1 (0.0)	(6.9)	1 1
O	t r e	h (9.)	0	1 1 0	(.4)	

All regi tered ub ect . s s s

Safety analy i et all regi tered ub ect who received at lea t s do e of tudy drug. Pharmacokinetic analy is et all regi tered ub ect who took at lea t one do e of tudy drug and who had at lea t one pla ma s concentration mea urement. s

Prior to do ing. s

Con ent di puted between parent prior to do ing. s s

Source End-of-Te t Table . . . and . . . , Appendi .s 1 2 1 1 1 1 2 1 1 1 2 1 2 1 1

b e a S m G s D o s a o P f c a c d B a e r p t r g t n i a t n i a h i il

/	r m t r e a a C C t r y e a 6 g 6 s Stati tic = (s s) (	C r t o o t y r s =) (	rt o o e t = a y (< s e t a y) < r 1) n (11) n	1 h r t o o t y (< s e t a y) < r 1	h t o e 1a <1 n 1	h n n
( )	**S e n**					
	Male	7 (6 .6)	6 (75.0)	8 (80.0)	(7 .4)	
	Female	4 (6.4)	(5.0)	(0.0)	82(27.6)	2 2
E, (c)	**t ty n h i i**					
	Not i panic or Latino s	4 (6.4)	(5.0)	4 (44.4)	2 (25.7)	
	i panic or Latino s	7 (6 .6)	6 (75.0)	5 (55.6)	8 (64.)	
	Mi ing ss	0	0			1
, (c)	**e a n R**					
	White	5 (45.5)	7 (87.5)	6 (60.0)	8 (6 .)	
	Black or African American	(7.)	(.5)	(2.0)	51(17.2)	1 1
	A ian s	(9.)	0	1 (0.0)	(6.9)	1 1
	American ndian or Ala ka Native I	0 s	0	0	0	
	Native awaiian or Pacific lander	(9.) Is	0	1 0 1	(.4)	
	Other	(9.)	0	1 (0.0)	(0.)	2 2
, s	**y r e e a g**					
	Mean (SD)	. (.)	9.0 (.7)	4.6 (1.8)	8.7 (51)	1 1
	Median	.0	9.5	4.5	9.0	1
	Min - Ma	5	6	1 7	17.1	12 1
, ( )	**t e k igh g**					
	Mean (SD)	5. 8 (.)	.8 (6.06)	69. 1 (9.15)	8.9 1(17.)	1 1 1
	Median	5.60	.7	65.85	280	
	Min - Ma	9.0 9.	8.6 67.4	4 .4 1 0 .5	9.0 0 .5	2 1

Table continued on next page

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/	r mtr ea a C C t ry e a 6 g 6 s Stati tic = (s = s) (	C rto o t y r s =) (	rto o et =oay (<s) n	1 h rto o et ay) <rl) n	h t o e 1a <1 n 1	h n n
,(c)	t em igh					
	Mean (SD)	97. (.76)	6.05 (7.5)	67.26 (915)	1 4.6 (1. 42)	1 1
	Median	96.50	4.75	6 .75	1 9.00	1 2
	Min - Ma	77.0 .0	6.0 67.9	57.4 181.0	77.0 8 .0	1 1 1
,(/)	Bm MI k g					
	Mean (SD)	6.9 (.58)	7. 7 (.59)	14. 92 (4.5)	19.79 (5.05)	2 2
	Median	6.	7.07	14. 42	18.67	2
	Min - Ma	.8 .6	.7 .9	6. 216	1.7 2.6	1 1

All regi tered ub ect . s s s

BM body ma inde (weight kg height m) Mss ma imum Min minimum

Source End-of-Te t Table . . . 12 1 2 1

P l b U e a r m sy s r T ad, E D e in a r n a t in g i n iag in 1

d c	C C 6 6 s = (=) ( )	t o o y r se t a oy <r ( )	rto o l 1 (n) 11 (n)	h rto o e t a oy <1) (n) n	h t o e 1a <1 n 1 n	h a n n
	c t ym e yt ou me e pu a h k i	i	i (.5)	(0.0)	1 12 (7.4)	1 1
cl	s t my e oe ue me e u una 4 (44.4)	i	i (5.0)	4 (40.0)	2 2 0 (7.0)	
s c	t m ae a pa n i 0		(5.0)	(0.0)	2 2 (.)	1 1
s	mm re ld ud n	i (.)	0	1 11 10	(.7)	
s	r N o m o u a a	(.)	(.5)	0	1 12 2 (4.8)	
O	t r e h	(.)	(5.0)	1 11 (0.0)	2 26 (.)	
s O	t r to m r d o u h	i 0	0	(0.0)	(.7)	1 1
ss	M n i g		0	2 0		

All regi tered ub ect . s s s

diopathic apla tic anemia, -linked adrenoleukodystrophy, hemophagocytic lymphohi tiocyto i , acute s lymphocytic leukemia relap e, acute myelobla tic leukemia, eve e combined immunodeficiency di ea e.

Meta tatic Ewing arcoma. s s s

Source End-of-Te t Table . . . , Appendi . .4. 12 1 2 1 1 2 1

Pl b C a S m m ry o in(a r/ s fa a)tr t u o lm sa Tr ngh v In fe i a go u d m a n P (A) S

s O v	6 r er en t r e a C rto o Stati tic 6 s 6 s r e	C rto o sa t < o y r e	rto o sa t <1 o y r e	1a <1
(/)	tr o m u gh L n g			
	D y a			
	n	9	8	9
	Mean (SD)	4 00 (440)	4 0 (2) 1	5 0 (01) 212 2
	C	4.	49.	44.6 1
	Median	4460	4 90	7 0 1
	Min Ma	0 6 0	700 8020 11	0 44 0 2 11
	D y a			
	n	9	8	8
	Mean (SD)	0 (7 0)	970 (6802) 1 1	7 0 (240) 1 2

Table continued on next page

s O v

6 r er emdt r ea a 6 Stati tic 6	C rto o s 6 o s r e	C rto o sa t < o y r e	rto o sa t < 1 o y r e	1 a < 1
C	5 .5	56.7 1	4 .6	
Median	6 0	400 1	80 2	
Min Ma	40 5950	770 5 110	7 0 4960 2	1

P AS all ub ect who took at lea t do e of tudy drug and who have at lea t pla ma concentration. s 1 s
Patient received 6 loading do e of i avuconazonium ulfate at 0 mg kg (if weight 40 kg) or at 71 mg (if weight 40 kg) on day and , and on day to 8 received 1 0 mg kg or 7 mg, re pectively, once daily. 2 s

C coefficient of variation Geo geometric Min minimum Ma ma imum P AS pharmacokinetic analy i et. s s s

Source End-of-Te t Table .4. 12 1

Pl bP e s S mPh ry c o Tin ca r mf a sa d a re mlt rs vze a dr n v i fo i I a o ubyl m a n
C P (A rt) o D y d a S a n h

C r mt r ea a Stati tic 6	C rto o s t 6 o y s r e	C 1 hrto o al s < t o y r e	hrto o a s < 1 t o y r e	1 a < 1
( ) D y a	1			
(/) m m a	L n g			

[redacted]

Cr mtr ea a Stati tic 6	C rto o s t 6 y s r e	C1 hrto o al s< t o y r e	hrto o a s<1 t o y r e	h 1a <1
tm a h				
n	9	8	7	
Median	.08	.08	.07	1
Min Ma	.0 . 5	.01 . 1	.01 2. 0 22	1 2

P AS all ub ect who took at lea t do e of tudy drug and who have at lea t pla ma concentration. s 1 s
Sub ect received 6 loading do e of i avuconazonium ulfate at 0 mg kg (if weight 40 kg) or at 71 mg (if weight 40 kg) on day and , and on day to 8 received 1 0 mg kg or 7 mg, re pectively, once daily. 2 s
C coefficient of variation Geo geometric Min minimum Ma ma imum P AS pharmacokinetic analy i et. s s s
Source End-of-Te t Table .4. 12 2

6 b Ov ev a r Ae ro Tm ts (Ev ast ev e) i de Ite Se n g n F

P c mbN Ercsud ea e Sbe Ctan e 6 6 s = (=) ( )	f nu rc6 g t o y r s ( ) = ( )	rto o 1 1 h rto o se t a o y <= (n)	h rto o s t a o y <1 r (n)	h t o e 1a <1 n	ha n 1 n
A E E y n T	7 (77.8)	8 (00.0)	0 (00.0)	1 5 (9 .6)	1 1
A DrEs r t e eu d a g	T(.)	(7.5)	4 (40.0)	0 (7.0)	
A s E E s Sr o u i T	(.)	4 (50.0)	5 (50.0)	(44.4)	
Dr s r E t Es e S r eu d a o ug	0 T	0	(0.0)	(.7)	1 1
A E Es l te d to lr d T o na a i g f 0 i h r t m te e a Tm		(.5)	(0.0) 1	12 (7.4)	1 1
A DrEs r t e eu d a te d g h t r d r o t m a e f a i h	T n i g	(.5)	(0.0) 1	12 (7.4)	1 1
s D t e a h	0	0	0	0	

SAF all regi tered ub ect who received at lea t s do e of tudy drug. A TEAE was defined a an AE s s ob erved after tarting admini tration of the tudy drug through follow-up. AE adver e event SAE eriou s adver e event SAF afety analy i et TEAE treatment-emergent adver e event. s
A rea onable po ibility that the event may have been au ed by the tudy drug a a e ed by the s s ss ss inve tigator. f relation hip i mi ing then it i con idered as drug-related. s s s
nclude SAE upgraded by the pon or ba ed on review of the pon or i t of Alway Seriou terms, if any s s s upgrade wa done. s
All reported death after the fir t tudy drug admini tration. s s s
Source End-of-Te t Table .6. . 12 1 1

b c e a r y A ro Tm ts (Ev ad F ec er O de Ite e rm g s un Sb t ne nf iu g i j
A C (A y r t m) te e r a o Sn Tm h F

A( ) v D ed C M C 1 R Cl s O s t m r e 6 a 6 n s Preferred term = (=) ( ) (	C rto o g t o y r s = ( ) ( )	hrto o te = o y (r <) (	1 hrto o et o y <1 n) n	h t o e 1a <1 n	ah n 1 n
Ov r e a ( ) (	) (	) (	6) 1	1 1	
c s o B y d s d t s a y t m a e n o d p d e h i i					
Thrombocytopenia	(.)	(.5)	(0.0)	6 (1 .1 2)	2 2
Anaemia	(.)	(.5)	(20.0 2) 2	6 (1 .1 2)	
Neutropenia	(.)	(5.0)	(10.0 1) 1	4 (24.8)	1 1
Febrile neutropenia	(.)	0	(20.0 2) 2	(.)	1 1

Table continued on next page

A( ) vD edC M C 1 R Cls Osst m re s a 6 ns Preferred term = (=)(( ) (	C rto o g t y s =) ( ) (	lrto o te = oy(r s) ( ) (	1 hrto o < et oy n) n n	lt o < 1 e 1 a	ah n < 1 n 1 n
c s	**s r d nd a d i i**				
Tachycardia	(.)	(5.0)	(10.0) 1	5 (28.3)	2 2
l s s	**s tr st ot ae r nd a d n ni i i**				
Diarrhoea	(.)	4 (50.0)	(20.0) 2	9 (.)	
Abdominal pain	(.)	(5.0)	(10.0) 1	6 (2 .2)	
Con tipation s	0	0	(0.0)	(7.4)	2 2
s c s	**s r e ers nd ast m ndtrdt a to i nae n i i i to d n n i i**				
Pyre ia	4 (44.4)	5 (6 .5)	5 (50.0)	4 (5 .2)	
Muco al inflammation s	5 (55.6)	4 (50.0)	(0.0)	(44.4)	
Fatigue	(.)	(.5)	(10.0) 1	5 (18.5) 2	
s s	**mm s y t m I eu nd d n i**				
Graft ver u ho t di ea e in kin	s s 0 s s	s s(5.0)	(0.0)	5 (28.3)	
Graft ver u ho t di ea e	s s(s) s	s (.5)	(20.0) 2	4 (14.8) 2	1 1
Engraftment yndrome	s0	(.5)	(0.0)	(1 .1) 2	2 2
c s	**s t s eo I ft d a no fia n i n in i**				
Clostridium difficile infection	(.)	(.5)	(10.0) 1	4 (14.8) 2	2 2
B viru infection	s (.)	(5.0)	10 11 1	(2 .2)	
uman herpe viru 6 infection	s0 s	(.5)	(0.0)	(1 .1) 2	2 2
Cytomegaloviru infection	0 s	0	(0.0)	(7.4)	2 2
, s c c s	**l ry c o b u r n jdor ape d n n ima ipg m o t o a p n i i**				
nfu ion related reaction I s	(.)	0	20 22 2	(7.4)	
Procedural nau ea	(s)	0	20 22 2	(7.4)	
Procedural vomiting	(.)	0	20 22 2	(7.4)	
s v s	**t t e o I a n n ig i**				
Electrocardiogram T prolonged	0	0	(0.0)	(7.4)	2 2
White blood cell count decrea ed	(.)	s0	(10.0) 1	(.)	2 2
Activated partial thrombopla tin time prolonged	0	s0	(0.0)	(7.4)	2 2
Prothrombin time prolonged	0	0	(0.0)	(7.4)	2 2
s	**t b e no Matr t d a o r nd n in n i i i**				
ypomagne aemia	(.)	(.5)	(10.0) 1	5 (18.5) 2	
yperglycaemia	(.)	0	(10.0) 1	(.)	2 2
ypoalbuminaemia	(.)	0	(20.0) 2	(.)	1 1
l sc s s s	**c c ot Mauevu oda a t ek e ne nnu i i r nd d i**				
Pain in e tremity	(.)	(.5)	4 (40.0) 1	6 (1 .1) 2	
Arthralgia	0	0	(0.0)	(.)	
Back pain	0	0	(0.0)	(7.4)	2 2
s s sv	**s r Nsey t m e nd d i**				
eadache	(.)	(.5)	20 22 2	(1 .1) 2	

Table continued on next page

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A( ) vD edC M C 1 R Cls Ost m re s a 6 ns Preferred term = (=)(( ) (	C rto o g t o s =) ( ) (	lrto o te = o d(r s) (	1 hrto o et o y) n n	lt o e 1 a	ah <1 n 1 n n
s c c s ys tr r rod d hi i i					
rritability I	(.)	0	(20.22 2	(.)	1 1
s esr rd a r rodna dR n i i					
Dy uria s	0	(7.5)	(0.0)	4 (4.8)	1 1
s, c t r t ry to sr oa m p adRead ahna i n i i s s r rd d i					
Epi ta i s	s (.)	(5.0)	(0.0)	6 (2 .2)	1 1
s c S s ss b std as to du n an r d d i i					
Pruritu	s (.)	0	(20.22 2	4 (4.8)	2 2
a h s	0	0	(0.0)	(7.4)	2 2
Urticaria	(.)	0	2 0 22 2	(7.4)	
l c Sr c ms u da ead or a dgie u p i					
Central venou catheter removal	0	(5.0)	0	(7.4)	
sc s s r r rd ad d i					
yperten ion	s (.)	(5.0)	0 11 1	(2 .2)	

SAF all regi tered ub ect who received at lea t s do e of tudy drug. A TEAE was defined a an AE s s ob erved after tarting admini tration of the tudy drug through follow-up. Within a y tem organ la , s s ub ect may have reported more than s preferred term. 1

AE adver e event SAF afety analy i et TEAE treatment-emergent adverse event. s

Source End-of-Te t Table .6. . 12 1 2

b l c e a r y e Dro T r u A of ent h as (nev ast e v ge) r d ente Se n g n F

A( ) vD edC M C 1 R Cls Ost m re s a 6 ns Preferred term = (=)(( ) (	C rto o g t o s =) ( ) (	lrto o te = o d(r s) (	1 hrto o et o y) n n	h o e 1 a	ah <1 n 1 n n
Ov r e a ( ) (	) (	) (	)		1
l s s str st ot ae r (rd ad n) ni	i i (	) (1	1 11 1)	1 1	
Diarrhoea	(.)	0	0 11 1	(.7)	
Nau ea s	0	0	(0.0)	(.7)	1 1
s s mm s y t m I eu rd d n (	i)	(	) 1 1		1
Graft ver u ho t di ea e	s s 0 s s s	(.5)	0	(1.7)	2
, s l ry c o b u (rj dr ap d) n n c c s m o t o a p n i	i ma ip g i	(	)		
nfu ion related reaction I s	(.)	0	2 0 22 2	(7.4)	
Procedural nau ea	(s .)	0	2 0 22 2	(7.4)	
Procedural vomiting	(.)	0	2 0 22 2	(7.4)	
s v s t t e o I a n n(ig	i) (	) (	)	1 1	11
Electrocardiogram T prolonged	0	0	(0.0)	(.7)	1 1
Cardiac murmur	0	(.5)	0	(1.7)	2
epatic enzyme increa ed	0 s	(.5)	0	(1.7)	2
s t b e o M a t r t d a o r d (d in n) i i	i (	) 1 1			1
Fluid imbalance	0	(.5)	0	(1.7)	2

Table continued on next page

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A( ) vD edC M C 1 R Cl s Os st m re s a 6 ns Preferred term = (=)(( ) (	C rto o g t y s =) ( ) (	lrto o te = oy rs) (	1 lrto o < et oy y n) n n	h o e 1 a	ah <1 n n 1 n n
s c S s ss b sd as (o u n an r i) m (i i) (1 11 1)					1
Pruritu generali ed s	0 s	0	(0.0)	(.7)	1 1
a h s	0	0	(0.0)	(.7)	1 1
a h follicular s	0	0	(0.0)	(.7)	1 1
Urticaria	(.)	0	0 11 1	(.7)	

SAF all regi tered ub ect who received at lea t s do e of tudy drug. A TEAE was defined a an AE s s ob erved after tarting admini tration of the tudy drug through follow-up. Within a y tem organ cla , s s ub ect may have reported more than s preferred term. 1

AE adver e event SAF afety analy i et TEAE treatment-emergent adverse event. s

Source End-of-Te t Table .6. . 12 1

A bl s E ve sa v r de tsc T e(tA e D) tu o t S n R nau i g in ni ni i F

r t m tA(r e ao P (n r rs e e r m d) f t D D o y a L T a S y D r d u u Do e s	) v D In s e d O p M	t S l e D o y O R t n m s o p e u t e o t ao d
rto o n 1 85.5 mg	epatic enzyme increa ed 1	5 ( ) ecovered e olved 1 1 1 Probable s s
rto o n 1 7 mg	Electrocardiogram T prolonged 2	7 5 (8) ecovered e olved 1 Po ible s

SAF all regi tered ub ect who received at lea t s do e of tudy drug. Cohort age group 6 to year Cohort 2 age group year 12 to 8 year . A treatment-emergent adverse event wa defined a an AE ob erved after tarting admini tration of the tudy drug through follow-up. 1 1 s s

AE adver e event SAF afety analy i et. s s s s s

Source Appendice . . . , . .5. , . .7.5 s 1 2 1 1 1 2 1 1 2

[redacted]

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min a o s an ou ou minsaou s an ou s an ou i sin ou s ou
f n amini oain afus u aminisoain us u so

N me 6S e a e oe a a e al f n dl cin au scal s o
an n in co o l s al aus v odu al f sinu as can als iu in ao s s c c

a o a a e a f o o lai n ni fus o u oinco insion uf sc so o
ain i i an l n fi f mi vac s n cazou n i m lfa cin usco loa iu uins ind c c s s
a i i f inv avi fon sal i a so a ils un i m s a sluc si alcm sal i n an in l in o o c c c u
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e o oea oe 6 m a o a N me va naznim lfa al l usco o u u s c u
a n m o u c c u

a o 6 ea me o a o 6S fapp a e maim m i f in a u o o o s
a s

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e a f o a a o

ff a f m al vi l fino offi a oa os m n lan nc cin i s s s s n s a f u s s I c s
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inf m ai n va ial al a in o loi n an ai o u s ao inf in u s so c o so

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f a i i n o am ca o oin o i m l vs l f co inc va on in o a a ou os s s
ima ama in i s o a ams c n in if ca n m if i a o s n in i o n n c a o o o s
a an f al in a a m l u s c s al co f m u as an u a c is a o
l a n i va n az l l ama os n a s c o m ca m n s co c in l o in u f in s al i a i c u l ai n c o u
ama in i m l f i n o va n c o an al o a m s o s i ai n ou s o a n s m o lin an o o s s o o
im l ai n in l ai n s a m a ins i o u o co c s o s

Sa a e o v l ama n n ai n as af i va s c o n az l o li o n vi s c o al o s I u u
n n ai n im fil d in ca an o m i l o al as l l a v l s a o a s i l s f o s a s a o s c
co m al i f o u a m a o n i i s i s ai d o in l c s a c m s f s c s s u u o
n m an m i m an m i o m i c an m i n i m o m an c m a i m m Ha n l n u o o
m i an m i n i m m an m a i m m al u l a u c c u

c lla s s n i a f o s s

va naznim lfa I usco o u us I
nv avi n a l i a I s u s s

ama in i aam ma co a cam ma lis u am mmaiz in si vi u sai i u s c s
a am v al iacio o laion ama in ic no u l oa v l co i cin oa n as a o ou
a n a l a ali asol lain asma sin ui no u l o m col vic o o
ama in i aam co c am ss s im ss a s

S mma of e o o a l f n d l cin a u sf c i s cm n ll o us
an vin u sc in os us ui n al a nu sc fs n o is in o os u s u co
af am a l i f s s s s v i a l a s n v u a l c a s m a in i m o s a m n co c u s
n i in a m a in c o i a u s a l i co a n c s s s m l u s a d c o s u s

m a i a a i i f o c c a c i c s o i n s a u l s c s c s m i n a l u s c s o
f m a l a n i u s c s i a a u i n s c f m s a s o o s

i m a n l i n i a n f u a o i n s o s a l u s c s m o l s n l m i a c u a o o u s
m m m n i a n i o c o o f l l o s s a u s c l m s i o l o m i a c u o c c u u s c s

i n o s u s c i n s i o o a n a m l l o i n s u s c s
i m a n a n o a m o s i n o u i u m s c a n s o o o
a n a m a n o s n i o s a n s c s

ff a a m o e a m o a m e

ff i a a i n f c i c n o v o u c o s o s

ama in i m m a f c o v a l c a s u a s o u o a n i u n i s a l s m m a s o s f u s
l a m a a m a in i a a m s f i v a c o n a z l c a f m l i d s i s c o i o n u a o f s a s s o u c
in a l i i n a a a a n n c f o o m a a n a s v a l c n o a u l i l u o s o
i i n n m i a n o u m a a c c i n o i l a a a s s c o s s o u s

a l a a m a in i a c a n f m c o f i n a l c l a i n a s m a in i n o u l i n o a i n c o a a c o c o o
f m i n v a n a n a b i n l l a o u s o o s s s a i a n i n o s
a l

a n f i n a l i m l a i n s o a i l s a a m i n i o o i s i n v a o n s l s a o u s o
a l a i m i n i m m o i f s i u o s

m i v a n a z n i m l f a f u s c o o i u i n u s o u n s c a i m s m l a i n a n a i l u o
m a i n n a n a m i n i c a n o s o s a m s o u s c

m i v a n a z n i m l f a f u s c o o i u i n u s o u s c s

i m i l a i i n u a i n s f i i n o v a s n s a l a m i n i a i n i n o u i a s o i a i n a n s o c
a l i m i l a i i o s i n s a l a i n a f o u v i s i n s u l i n i a l s m m o n a c c c o o
f a m i n i a i n i n o u a i o a i n a n s o i c n i n o v a s n a n c a l a n o u n l s o s
i i n a n a i l i f a m i n i s a i c n i a b i n a l s o o u s s o u s

Safe e v n f m v i i a s n l v s i i s o a c u o i c l a s u s s s u

c l l a s s n i a f o s s

[redacted]

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f n fala f u c io a s 6 u s c m l v s l in a m in l a m n i s co
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l a i n u m f n l o c s u m i i n o a m s n a a a o f u s c o o
in n n l a o I a o n i n m a m v s s a l v o m i i n u s c o
i a a a a m n a a a c m s m m n c l a o c o o l a s u s u
l in s o o c o o s

v a l f i n a o u a s c s v n c s u m s f s n i n a m o s u
i n l a m n a s i a c o o a l u s c i n s o s a c u s c
n m f f i n v i i a l v n o a v o s l u s s o

n a m n l u a s c o a a i a n a s o u a v m i i n s c a n c i a u s o
n a i n a a l i o l i n a m o n i o a o l a i l c o a s s o s s o u s u
f i a a m i l i n v i o f s a a i s a n a a a n v o n s i o n c n u i s v o c o s
f n a a v m i i n a m o i s a u l s c i n i n i n a i n f u s n o s a u o o u s u o u
v a m a l l v n c o n i v i s c o s a l o n s i n u s s c a s o l s o v i a i n o o o c o
v v n l i n i n i s n i n a s i n s u s f c o s u o i n o a m i n s c s o o
a l n i n i n u s c o n o a f c i l o s i n i n i o a i n c f u s c o s u
v n u s i u i l l a s c o s o i s s a i o u a s n n u a c s o
n i n a o a u l s c i l a o a m i n a m i n a m f a a a a a a m i n a m s f a s s o
i n a n a v n c s o f m a v i s a n o n o i o s a l c a s o o
i a i a n n u a c a a s v n o n s i v i n s a c o n s f o o s o
a l i l i n o i n u s a c m i n o a o a i n f c m a v i n a o a o a s o
n i i l l c a o s o o i s s a i o u a s n n u a c v s n a o n i c o s
v n a n o s a o a l I l o o i n o v m u s c a l i n f l a m m c a i n s a l u c o s o
m i i n a a a u n c o i s o s l a c o s s i o a i o u a s n n u a c v n s o
a n i v n a c o s s o s o

N S N S

- i a f i i n i s a f s a n s u s a m a o n i f s a l i v a n a c o n i m c l f o a s o a u s c o o u u
  f m a l i n v i a i n i l o n s c
- n a m a n a a n m a n u m i a l i n n u c a o u u s c s o
  a a n n n m a m n a l s a n s o a c i n c o i a n a l i i m i l a c o n c i a i n s s s
  a a n i n a f i s f l l s s i n i n v a o n u s i n o o l a i n o u c s s o u o
  a m a i n i m l n f i m c o a c a l f o m c b a i n a n a o i l i z o i n u o n o s u s u s
  v i i m i l a o i o u a s l s n s a o a o u s s u i n s f a f u a n o u s u u s
  f f i a l i n i a l i a l c c c s
- v a n a z n i m l f a h u s c o a l o a f u a n u s l l l a s i n i s c i n n a f u s s c s
  i n f m a i n i f i i c a i o l a i s n c c a a n v i c o f u m o a a f n o a n s u
  f v a o a o s n s n l i n c m i a l s n i i n u f c c l c a i n o o s u s

c lla s s n i a f o s s

va naznim lfa I uscoouus I
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n i al m a m ncs co
ou c nui

c lla s s n i a f o ss

va nazni m lfa I usco o u us I
nv avi n a i a I su s s
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v af ain aminci aisn f s sc fl b us u ou o o u
av v n i av vs n afsu an al i s ansn m sns sav
v n
a n al i ili a vonsma ova ss n a a ca u s us u s ss ss
inv i a f lain i i mi ins o lh i i on i s as ss la cos s sa
n l a I c u n s aus n v i f os ons lis o f l ao i os ons ifs ons s ou s
a a n u os
ll a af fi o aminsi ai n sus u so
n f al ou c o

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ll a s sn i a f o ss

[redacted]

a e e e e e o a o S

ea me op	**e efe e e m** o s	**e S p a a oe a**	**ome**	**ea o p oS**	
o o					
a m a m	a sa mi in i a	u o	s v v v v v v	cio l cio l cio l	o s o s o s
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o o					
a m a m	a inflsmm ai n	uco s	o v v	cba	o s

al i v als au sc fso c soa os us u o oa ou o
a o o a amn n m n av s v n a fin a am s v afs s o
a in a mini ai n f s scf lb us u ou o o u
av v n af an a i s s sss
n i ou c c s