!" #&/

4;O <548G=>3> 70AB>AC20==O ;V:0@AL:>3> 70A>1C

!

(OMNIC OCAS)

!:;04:

4VNG0 @5G>28=0: B078=C 3V4@>E;>@84; 1 B01;5B:0 78=C 3V4@>E;>@84C;

4>?>28=8: <0:@>3>; 8000, <0:@>3>; 7000000, <03=VN AB50@0B, 2>40 >G8I5=0, >?04@V 6>2B89 03F22733.

V:0@AL:0 D>@<0. "01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, ?@>;>=3>20=>W 4VW 7 ?5@>@0;L=>N A8AB5<>N :>=B@>;L>20=>W 01A>@1FVW.

A=>2=V DV78:>-EVABV: B01;5B:8 :@C3;V, 42>>?C:;V, 2:@8BV 6>2B>N ?;V2:>2>N >1>;>=:>N,<0@:>20=V B8A=5==O< «04».

$0@<0:>B5@0?52B8G=0 3@C??0. 0A>18, I> 70AB>A>2CNBLAO ?@8 4>1@>O:VA=V9 3V?5@?;07VW ?5@542>W 70;>78. =B03>=VAB8 α_1-04@5=5@3VG=8E @5F5?B>@V2. >4 "% G04C A02.

$0@<0:>;>3VG=V 2;0AB82>ABV.

$0@<0:>48=0

<=V: :0A 281V@:>2> V :>=:C@5=B=> 1;>:CT ?>ABA8=0?B8G=V α_1-04@5=>@5F5?B>@8, 7>:@5<0 α_{1A} B0 α_{1D}, I> 7=0E>4OBLAO C 3;04:V9 2>W 70;>78, H89:8 A5G>2>3> AB0B8G=>W G0AB8=8 C@5B@8. &5 ?@872>48BL 4> 7=865==O B>=CAC 3;04:>W 2>W 70;>78, H89:8 A5G>2>3> AB0B8G=>W G0AB8=8 C@5B@8 B0 ?>;V?H5==O 284V;5==O A5GV.

4=>G0A=> 7<5=HCNBLAO A8<8 >1AB@C:FVW B0 ?>4@07=5==O, ?>2O70=V 7 4>1@>O:VA=>N 3V?5@?;07VTN ?5@542>W 70;>78 (CB@C4=5==O ?>G0B:C A5G>28?CA:0==O, ?>A;01;5==O AB@C<5=O A5GV, :@0?0==O ?VA;O 70:V=G5==O A5G>28?CA:0==O, 2V4GCBBO =5?>2=>3> A?>@>6=5==O A5G>2>3> 7828 4> A5G>28?CA:0==O, ?>7828 4> A5G>28?CA:0==O 2 =VG=89 G0A, =52V4:;04=VABL A5G>28?CA:0==O).

40B=VABL α_{1A}-04@5=>1;>:0B>@V2 7<5=HC20B8 0@B5@V0;L=89 B8A: ?>2O70=0 7V 7<5=H5==O< ?5@8D5@8G=>3> >?>@C. <=V: :0A C 4>1>2V9 4>7V 0,4 <3 =5 A?@8G8=OT :;V=VG=> 7=0GCI5 7=865==O A8AB5<=>3> 0@B5@V0;L=>3> B8A:C (") O: C E2>@8E =0 0@B5@V0;L=C 3V?5@B5=7VN, B0: V C ?0FVT=BV2 7 =>@<0;L=8< ?>G0B:>28< ".

$0@<0:>:V=5B8:0.

1A>@1FVO. <=V: :0A O2;OT A>1>N B01;5B:C ?@>;>=3>20=>W 4VW 7 :>=B@>;L>20=8< 282V;L=5==O< =0 >A=>2V <0B@8:AC 7 28:>@8AB0==O< 35;N =5V>==>3> B8?C. $>@<0 :0AC 70157?5GCT B@820;5 B0 ?>2V;L=5 282V;L=5==O B078=C, I> 40T 5:A?>78FVN 7V A;01:8<8 :>;820==O<8 ?@>BO3> < 24 3>48=. VA;O ?5@>@0;L=>3> ?@89>78=C 01A>@1CTBLAO 2 :8H5G=8:C. (284:VABL V @>7@1FVW B01;5B>: ?@>;>=3>20=>W 4VW =5 7< 68@C. !BC?V=L 2A<>:BC20==O ?V428ICTBLAO =0 64 % B0 149 % (AUC B0 !$_{<0:A}$ 2V4?>2V4=>) ?@8 ?@89>:8< 2< 68@C ?>@V2=O=> 7 ?@89><>< =0BI5. "078= 45<>=AB@CT ;V=V9=C D0@<0:>:V=5B8:C.

VA;O >4=>@07>2>3> ?@89><=V:C :0A =0BI5 <0:A8<0;L=0 :>=F5=B@0FVO 0:B82=>W @5G>28=8 C ?;072V A?>AB5@V30TBLAO G5@57 6 3>48=. #@V2=>206=>AO30TBLAO =0 G5B25@B89 45=L ?@89>=F5=B@0FVW A?>AB5@V30TBLAO G5@57 4-6 3>48= =570;56=> 2V4 ?@89>=F5=B@0FVW C ?;072V ?V428ICTBLAO 7 ?@81;87=> 6 =3/<; ?VA;O ?5@H>3> ?@89> 11 =3/<; C @V2=>206=>

/: @57C;LB0B B@820;>3> 282V;L=5==O, =09=86G89 @V25=L :>=F5=B@0FVW B078=C C ?;0728BL 40 % <0:A8<0;L=>W :>=F5=B@0FVW =570;56=> 2V4 ?@89>

>7?>4V;. 2O7C20==O 7 1V;:0<8 ?;07<8 99 %. 1T< @>7?>4V;5==O =57=0G=89 (?@81;87=> 0,2 ;/:3).

5B01>;V7 "078=C 3V4@>E;>@84 <0T =87L:89 5D5:B ?5@H>3> ?@>E>465==O, ?>2V;L=> <5B01>;V7CNG8AL. V;LH0 G0AB8=0 0:B82=>W @5G>28=8 ?@8ACB=O 2 :@>2V C =57;V7CTBLAO C ?5GV=FV. 57C;LB0B8 *in vitro* ?>:07CNBL, I> CYP3A4 V B0:>6 CYP2D6 2:;NG0NBLAO C <5B01>;V7<, V=HV V7>D5@<5=B8 CYP =57=0G=> 2?;820NBL =0 B078=. @83=VG5==O <5B01>;V7CNG8E D5@<5=BV2 CYP3A4 V CYP2D6 <>65 ?@8725AB8 4> ?V428I5==O 5:A?>78FVW B078=C 3V4@>E;>@84C (482. @>74V;8 «A>1;82>ABV 70AB>AC20==O», «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»). >45= 7 <5B01>;VBV2 =5 O2;OTBLAO 0:B82=VH8< 70 4VNGC @5G>28=C.
82545==O. "078= B0 9>3> <5B01>;VB8 282>4OBLAO 2 >A=>2=>4 =0?V2282545==O B078=C ?@8 >4=>@07>2>206=>28BL 19 V 15 3>48= 2V4?>2V4=>.

;V=VG=V E0@0:B5@8AB8:8.

>:070==O.

V:C20==O A8282V4=8E H;OEV2 ?@8 4>1@>O:VA=V9 3V?5@?;07VW ?@>AB0B8.

@>B8?>:070==O.

V?5@GCB;82VABL 4> B078=C 3V4@>E;>@84C, 2:;NG0NG8 <548:0<5=B>7=>-V=4C:>20=89 0=3V>=52@>B8G=89 =01@O:, 01> 4> 1C4L-O:>W 7 4>?> 28=; =0O2=VABL 2 0=0<=57V >@B>AB0B8G=>W 3V?>B5=7VW; BO6:0 ?5GV=:>20 =54>AB0B=VABL.

70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.

>A;V465==O 270T<>4VW 28:>=C20;8AO BV;L:8 C 4>@>A;8E.
@8 >4=>G0A=>AC20==V B078=C 3V4@>E;>@84C 7 0B5=>;>;><, 5=0;0?@8;><, 01> B5>DV;V=>< ;V:0@AL:>W 270T<>4VW =5 2V47=0G0;>AO.
4=>G0A=5 70AB>AC20==O 7 F8<5B848=>< ?V428ICT, 0 7 DC@>A5< 7=86CT :>=F5=B@0FVN B078=C C ?;072V, 0;5 >A:V;L:8 FV @V2=V 70;8H0NBLAO C <560E =>@<8, C A?5FV0;L=V9 :>@5:FVW 4>7C20==O B078=C =5<0T =5>1EV4=>ABV.
# 4>A;V465==OE *in vitro* 4V075?0<, ?@>?@0=>;>;, B@8E;>@<5BV0784, E;>@<048=>=, 078=C C ?;072V ;N48=8. >4V1=8< G8=>< B078= =5 7?@0=>;>;C, B@8E;>@<5BV0784C B0 E;>@<048=>=C C ?;072V ;N48=8.
@>B5 48:;>D5=0: B0 20@D0@8= <>6CBL ?V428IC20B8 H284:VABL 5;V78=C.
4=>G0A=5 70AB>AC20==O B078=C 3V4@>E;>@84C 7 A8;L=8<8 V=3V1VB>@0<8 CYP3A4 <>65 ?@8725AB8 4> 71V;LH5==O 2?;82C B078=C 3V4@>E;>@84C. 4=>G0A=5 70AB>AC20==O 7 :5B>:>=07>;>< (2V4><89 A8;L=89 V=3V1VB>@ CYP3A4) ?@872>48;> 4> 71V;LH5==O AUC V !max 4> 2,8 V 2,2 2V4?>2V4=>.
"078=C 3V4@>E;>@84 =5 A;V4 ?@87=0G0B8 C :><1V=0FVW 7 A8;L=8<8 V=3V1VB>@0<8 CYP3A4 C ?0FVT=BV2 7 =87L:8< <5B01>;V7<>< CYP2D6.
"078=C 3V4@>E;>@84 A;V4 70AB>A>2C20B8 7 >15@56=VABN C :><1V=0FVW 7 A8;L=8<8 V ?>
4=>G0A=5 70AB>AC20==O B078=C 3V4@>E;>@84C V ?0@>:A5B8=C (A8;L=89 V=3V1VB>@ !YP2D6) ?@872>48;> 4> 71V;LH5==O !max V AUC 4> 1,3 V 1,6 2V4?>2V4=>, 0;5 F5 =5 T :;V=VG=> 7=0GCI8
4=>G0A=5 70AB>AC20==O 7 V=H8<8 α_1-04@5=>1;>:0B>@0<8 <>65 ?>A8;N20B8 3V?>B5=782=89 5D5:B.

A>1;82>ABV 70AB>AC20==O.

/: V ?@8 70AB>AC20==V V=H8E α_1-04@5=>1;>:0B>@V2, 2 >:@5<8E 28?04:0E ?@8 70AB>AC20==V <=V: :0A <>6;825 7=865==O 0@B5@V0;L=>3> B8A:C, I> <>65 @V4:> ?@872>48B8 4> 2B@0B8 A2V4><>ABV. @8 ?>O2V ?5@H8E >7=0: >@B>AB0B8G=>W 3V?>B5=7VW (70?0<>@>G5==O, A;01:VABL) ?0FVT=B<0T ?@8AVAB8 G8 ?@89=OB8 3>@87>=B0;L=5 ?>;>65==O 4> 7=8:=5==O 28I573040=8E A8

5@54 B8< O: @>7?>G0B8 ;V:C20==O ?@5?0@0B>< <=V: :0A, A;V4 ?@>9B8 <548G=5 >1AB565==O 7 <5B>N 28O2;5==O V=H8E AC?CB=VE 70E2>@N20=L, I> <>6CBL A?@8G8=8B8 B0:V A02>W 70;>78. 5@54 ?>G0B:>< ;V:C20==O =5>1EV4=> ?@>25AB8 @5:B0;L=5 >1AB565==O ?5@542>W 70;>78 B0 ?@8 =5>1EV4=>ABV B5AB =0 287=0G5==O @V2=O A?5F8DVG=>3> 0=B835=C ?5@542>W 70;>78 (PSA) 4> ?>G0B:C B0 G5@57 >4=0:>2V ?@>
@87=0G0B8 ?@5?0@0B ?0FVT=B0< V7 BO6:>N AB04VTN =8@:>2>W =54>AB0B=>ABV (:;V@5=A :@50B8=V=C <10<;/E2) =5>1EV4=> 7 >A>1;82>N >15@56=VABN, >A:V;L:8 :;V=VG=8E 4>A;V465=L 4;O B0:8E ?0FVT=BV2 =5 ?@>2>48;8.
45O:8E ?0FVT=BV2, O:V ?@89<0;8 01> ?@89<0NBL B078=, ?V4 G0A EV@C@3VG=>3> 2B@CG0==O 7 ?@82>4C 2840;5==O :0B0@0:B8 V 3;0C:><8 2V47=0G02AO A8=4@>< 0B>=VG=>W 7V=8FV (IFIS, 20@V0=B A8=4@>W 7V=8FV), I> <>65 AB0B8 ?@8G8=>N 71V;LH5==O :V;L:>ABV CA:;04=5=L ?V4 G0A G8 ?VA;O ?@>2545==O B0:>W >?5@0FVW.
/: ?@028;>, 70 1-2 B86=V ?5@54 ?@>2545==O< >?5@0FVW 7 ?@82>4C 2840;5==O :0B0@0:B8 V 3;0C:><8 @5:><5=4CTBLAO ?@8?8=8B8 ;V:C20==O B078=><, ?@>B5 :>@8ABL 2V4 ?@8?8=5==O ;V:C20==O B078=>< =0 40=89 G0A B>G=> =5 2AB0=>2;5=0. @> A8=4@>< 0B>=VG=>W 7V=8FV ?>2V4><;O;>AO B0:>6 C ?0FVT=BV2, O:8< ?@8?8=8;8 70AB>AC20==O B0AC;>78=C ?@>BO3>< B@820;>3> G0AC 4> ?@>2545==O >?5@0B82=>3> 2B@CG0==O 7 ?@82>4C :0B0@0:B8.
?0FVT=BV2 ?5@54 ?;0=>2>N >?5@0FVTN :0B0@0:B8 G8 3;0C:><8 =5 @5:><5=4CTBLAO @>7?>G8=0B8 ?@89>< B078=C 3V4@>E;>@84. @8 ?V43>B>2FV 4> >?5@0FVW EV@C@38 B0 >DB0;L<>;>38 <0NBL 4V7=0B8AO, G8 ?@89<02 (01> ?@89<0T) ?0FVT=B B078= 7 <5B>N ?>?5@5465==O <>6;828E CA:;04=5=L, ?>2O70=8E V7 IFIS.
"078=C 3V4@>E;>@84 =5 A;V4 ?@87=0G0B8 C :><1V=0FVW 7 A8;L=8<8 V=3V1VB>@0<8 CYP3A4 ?0FVT=B0< 7 =87L:8< <5B01>;V7<>< CYP2D6.
"078=C 3V4@>E;>@84 A;V4 70AB>A>2C20B8 7 >15@56=VABN C :><1V=0FVW 7 A8;L=8<8 V ?>
=>4V <>6;82> 7=09B8 70;8H:8 B01;5B:8 C D5:0;VOE.
>2V4><;O;8 ?@> 28?04:8 0;5@3VG=8E @50:FV9 =0 B078= C ?0FVT=BV2 7 =0O2=VABN 2 0=0<=57V 0;5@3VW =0 AC;LD0=V;0B@815@56=>ABV ?@8 70AB>AC20==V B078=C 3V4@>E;>@84C ?0FVT=B0<, C O:8E @0=VH5 2V47=0G0;0AO 0;5@3VO =0 AC;LD0=V;0

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.
<=V: :0A =5 ?>:070=89 4;O 70AB>AC20==O 6V=:0
$5@B8;L=VABL
V4 G0A :;V=VG=8E 4>A;V465=L B078=C ?@>BO3>< :>@>B:>3> B0 B@820;>3> G0AC 2V47=0G0;8AO ?>@CH5==O 5O:C;OFVW. 8?04:8 ?>@CH5==O 5O:C;OFVW, @5B@>3@04=>W 5O:C;OFVW V =54>AB0B=L>W 5O:C;OFVW 2V47=0G0;8AO C ?VA;O@5TAB@0FV9=4V.

40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B>< 01> V=H8<8 <5E0=V7<0<8.
>A;V465==O 2?;82C ?@5?0@0BC =0 740B=VABL :5@C20B8 02B>B@0=A?>@B>< 01> <5E0=V7<0<8 =5 ?@>2>48;8. 4=0: ?0FVT=B8 <0NBL 1CB8 ?>?5@5465=V ?@> <>6;82VABL 28=8:=5==O 70?0<>@>G5==O.

!?>AV1 70AB>AC20==O B0 4>78.
5:><5=4>20=0 4>70 1 B01;5B:0 I>45==>, =570;56=> 2V4 ?@89>2B0B8 FV;>N, =5 @>7;076>2CNG8 WW, >A:V;L:8 F5 1C45 ?5@5H:>460B8 4>23>B@820;>=B@>;L>20=>3> V=3@54VT=B0. "@820;VABL ;V:C20==O 2AB0=>2;NTBLAO V=482V4C0;L=>.
0FVT=B0< V7 =8@:>2>N =54>AB0B=VABN =5 ?>B@V1=0 :>@5:FVO 4>78. 0FVT=BV2 V7 ?>N B0 A5@54=L>3> ABC?5=O BO6:>ABV ?5GV=:>2>N =54>AB0B=VABN =5 ?>B@V1=0 :>@5:FVO 4>78 (482. B0:>6 «@>B8?>:070==O»).

VB8.
@5?0@0B =5 70AB>A>2C20B8 4VBO
57?5:C B0 5D5:B82=VABL 70AB>AC20==O B078=C 4VBO< =5 >FV=N20;8.

5@54>7C20==O.
!8<8.
5@54>7C20==O B078=>< 3V4@>E;>@84>< <>65 ?>B5=FV9=> A?@8G8=8B8 BO6:C 3V?>B5=782=C 4VN. "O6:0 3V?>B5=782=0 4VO 2V47=0G0;0AO ?@8 @V7=8E ABC?5=OE ?5@54>7C20==O.
V:C20==O.
28?04:C @V7:>3> 7=865==O B8A:C 2=0A;V4>: ?5@54>7C20==O A;V4 ?@>2>48B8 ?V4B@8: 28A>:>3> ABC?5=O 72O7C20==O B078=C 7 1V;:0<8 ?;07 <8 :@>2V ?@>2545==O 35<>4V0;V7C T =02@O4 G8 4>FV;L=8
<5B>N ?@8?8=5==O ?>40;LH>3> 2A<>:BC20==O ?@5?0@0BC <>6=0 HBCG=> 28:;8:0B8 1;N20==O. @8 ?5@54>7C20==V 7=0G=>W :V;L:>ABV ?@5?0@0BC ?0FVT=BC =5>1EV4=> ?@><8B8 H;C=>: V7 70AB>AC20==O< 0:B82>20=>3> 2C3V;;O B0 =87L:>>A<>B8G=8E ?>A;01;N20;L=8E 70A>1V2, B0:8E O: AC;LD0B =0B@VN.

>1VG=V @50:FVW.

!8AB5<0 >@30=V7	'0AB> (>1/100, <1 /10)	5G0AB> (>1 /1000, <1/100),	V4:> (>1/10000, <1 /1000)	C65 @V4:> (<1/10000)	52V4><> (=5 <>6;82> >FV=8B8 ?@8 =0O2=>ABV 4>ABC?=8E 40=8E)
52@>;>3VG=V @>7;048	0?0<>@>G5==O (1,3 %)	>;>2=89 1V;L	5?@8B><=VABL		
1>:C >@30=V2 7>@C					0BC<0=5==O 7>@C*, ?>@CH5==O 7>@C*
1>:C A5@FO		V4GCBBO A5@F518BBO			
!C48==V @>7;048		@B>AB0B8G=0 3V?>B5=7VO			
5A?V@0B>@=>-<54V0AB8=0;L=V @>7;048		8=VB			>A>20 :@>2>B5G0*

(;C=:>2>-:8H:>2V @>7;048 **>7;048 7 1>:C H:V@8 B0 A;87>28E >1>;>=>:**		0?>@, 4V0@5O, =C4>B0, 1;N20==O 8A8?0==O, A25@1V6, :@>?82 O=:0	=3V>=52@>B8G=89 =01@O:	!8=4@>< !BV25=A0-6>=A>=0	!CEVABL C @>BV* C;LB8D>@<-=0 5@8B5<0*, 5:AD>;V0B82-=89 45@ <0B8B*
5?@>4CB82=V ?>@CH5==O	>7;048 5O:C;OFVW, 2:;NG0NG8 @5B@>3@04=C 5O:C;OFVN V =54>AB0B=VABL 5O:C;OFVW			@V0?V7<	
030;L=V @>7;048		AB5=VO			

*- 2V47=0G0;8AO C ?VA;O@5TAB@0FV9=>4V V4 G0A ?VA;O@5TAB@0FV9=>3> =03;O4C >?8A0=V 28?04:8 V=B@0>?5@0FV9=>W =5AB01V;L=>ABV @094C6=>W >1>;>=:8 >:0 (A8=4@≍ 72C65=>W 7V=8FV) ?@8 >?5@0FVW 7 ?@82>4C :0B0@0:B8 B0 3;0C:><8 C ?0FVT=BV2, O:V ?@89<0;8 B078= (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

VA;O@5TAB@0FV9=89 4>A2V4: :@V< 28I52:070=8E ?>1VG=8E @50:FV9 ?>2V4><;O;>AO ?@> 28?04:8 DV1@8;OFVW ?5@54A5@4L, 0@8B5. @> 707=0G5=V 28?04:8 ?>2V4><;O;>AO A?>=B0==>, G0AB>BC ?>2V4><;5=L B0 @>;L B078=C C FL>

"5@ABV. 3 @>:8.

#<>28 715@V30==O. 15@V30B8 C =54>ABC?=> 15@V30B8 ?@8 B5

#?0:>2:0. > 10 B01;5B>: C 1;VAB5@V, ?> 3 1;VAB5@8 2 :0@B>==V9 :>@>1FV.

0B53>@VO 2V4?CA:C. 0 @5F5?B>

8@>1=8:. AB5;;0A $0@<0 .@>? .., V45@;0=48.

VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A0 20465==O 4VO;L=>ABV.

AB5;;0A $0@<0 .@>? ..: %>35<0B 2, 7942 5??5;, V45@;0=48/Astellas Pharma Europe B. V.: Hogemaat 2, 7942 JG Meppel, the Netherlands.

0O2=8:. AB5;;0A $0@<0 .@>? ..

VAF57=0E>465==O 70O2=8:0. !8;L2VCA253, 62, 2333 5945=, V45@;0=48/Sylviusweg, 63, 2333 Leiden, the Netherlands.

28?04:C 28=8:=5==O ?>1VG=8E 5D5:BV2 ?@>A8<> =0?@02;OB8 V=D>@<0FVN 4> ?@54AB02=8FB20 AB5;;0A $0@<0 .@>? . . =0 04@5AC: 04050, <. 8W2, 2C;. 8<>=5=:0, 13, :>@?. 7-, >DVA 41, B5;.: 044-490-68-25, D0:A: 044-490-68-26.