

!" #&/
4;O <548G=>3> 70AB>AC20==O ?@5?0@0BC

!"®
(VESTINORM)

!::04:

4VNG0 @5G>28=0: betahistine;

1 B01;5B:0 E;>@84C 8 <3 01> 16 <3, 01> 24 <3 C ?5@5@0EC20==V =0 100 % ACEC @5G>28=C;
4>?>28=8: F5;N;>70 :@8AB0;VG=0, =0B@VN :@>E<0;L3;V:>;OB (B8?), :@5<=VN 4V>:A84 :>;>W4=89
1572>4=89, ?>2V4>=, <03=VN AB50@0B.

V:0@AL:0 D>@<0. "01;5B:8.

\$0@<0:>B5@0?52B8G=0 3@C?0. 0A>18 4;O ;V:C20==O 25AB81C;O@=8E ?>@CH5=L.
>4 "C N07! 01.

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

>:070==O.

%2>@>10 B0 A8=4@< 5=LT@0, O:V E0@0:B5@87CNBLAO B0:8<8 >A=>2=8<8 A8<0<8:
70?0<>@>G5==O<, I> V=>4V AC?@>2>46CTBLAO =C4>B>N V 1;N20==O<;
7=865==O< A;CEC (BC3>2CEVABN);
HC<>< C 2CE0E.

!8<0B8G=5 ;V:C20==O 25AB81C;O@=>3> 70?0<>@>G5==O @V7=>3> ?>E>465==O.

@>B8?>:070==O.

V?5@GCB;82VABL 4> 1C4L-O:>3> 7 :>5=BV2 ?@5?0@0BC. \$5>E@><>F8B><0.

!?!>AV1 70AB>AC20==O B0 4>78.

@87=0G0NBL 4>@>A;8< 2=CB@VH=L>. >1>20 4>70 AB0=>28BL 2448 <3, @V2=> @>7?>4V;5=0 4;O
?@89>BO3>< 4>18.

"01;5B:8 ?> 8 <3	"01;5B:8 ?> 16 <3	"01;5B:8 ?> 24 <3
1-2 B01;5B:8 3 @078 =0 4>1C	½1 B01;5B:0 3 @078 =0 4>1C	1 B01;5B:0 2 @078 =0 4>1C

"01;5B:8 ?@89<0NBL ?VA;O W48, =5 @>76>2CNG8.

>7C V B@820;VABL B5@0?VW 287=0G0T ;V:0@ V=482V4C0;L=> 70;56=> 2V4 5D5:B82=>ABV
B5@0?VW. <5=H5==O A8;8 A?>AB5@V30TBLAO BV;L:8 ?VA;O 2-3 B86=V2 ;V:C20==O. 09:@0IV
@57C;LB0B8 A?>AB5@V30NBLAO ?@8 ?@89>BO3>< :V;L:>E ;V:C20==O ?@87=0G8B8 =0 ?>G0B:C
70E2>@N20==O, <>6=0 70?>1V3B8 ?@>3@5AC20==N 9>3> V/01> 2B@0BV A;CEC =0 ?V7=VE
AB04VOE.

0FVT=B8 ;VB=L>3> 2V:C. >@5:FVO 4>78 4;O ?0FVT=BV2 FVTW 3@C?8 =5 ?>B@V1=0.

8@:>20 =54>AB0B=VABL >@5:FVO 4>78 =5 ?>B@V1=0.

5GV=:>20 =54>AB0B=VABL >@5:FVO 4>78 =5 ?>B@V1=0.

>1VG=V @50:FVW.

I>:C B@02=>3> B@0:BC: =C4>B0, 48A?5?AVO; A:0@38 =0 =57=0G=V @>7;048 H;C=:0 (1;N20==O,
1V;L C 682>BV, 74CBBO 682>B0 B0<5B5>@87<). &V ?>1VG=V 5D5:B8 70728G09 7=8:0NBL ?@8 ?@89>
?VA;O 7<5=H5==O 4>78.

I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L.

I>:C VW A8AB5<8: @50:FVW 3V?5@GCB;82>ABV, =0?@8::04 0=0DV;0:AVO.

I>:C H:V@8 V ?V4H:V@=>W ;;VB:>28=8: @50:FVW 3V?5@GCB;82>ABV H:V@8 B0 ?V4H:V@=>W
68@>2>W ;;VB:>28=8, 7>:@5<0 0=3V>=52@>B8G=89 =01@O.;, 28A8?0==O, A25@1V6 V :@>?82O=:0.

5@54>7C20==O.

V4><> :V;L:0 28?04:V2 ?5@54>7C20==O 15B03VAB8=C. # 45O:8E ?0FVT=BV2 A?>AB5@V30;8AO ;53:V
V ?> A8<8 (=C4>B0, A>=:82VABL, 1V;L C 682>BV) ?VA;O ?@89>2 4>70E 4> 640 <3. !5@9>7=VHV
CA:;04=5==O (AC4><8, A5@F52>-;535=52V CA:;04=5==O) A?>AB5@V30;8AO ?@8 =02<8A=>7
15B03VAB8=C, >A>1;82> C ?>T4=0==V 7 ?5@54>7C20==O< V=H8E ;V:0@AL:8E 70A>1V2.
V:C20==O ?5@54>7C20==O
V:C20==O ?5@54>7C20==O ?>28==> 2;;NG0B8 AB0=40@B=V ?V4B@848.

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

03VB=VABL. 5<0T 4>AB0B=VE 40=8E I>4> 70AB>AC20==O 15B03VAB8=C 203VB=8< 6V=:0
57C;LB0B8 4>A;V465=L =0 B20@8=0E T =54>AB0B=V<8 4;O >FV=:8 2?;82C =0 ?5@51V3 203VB=>ABV,
@>728B>: 5<1@V>=0?;>40, ?>;>38 B0 ?>AB=0B0;L=89 @>728B>.: >B5=FW9=89 @878: 4;O ;N48=8
=52V4><89. 5B03VAB8= =5 A;V4 70AB>A>2C20B8 C ?5@V>4 203VB=>ABV, 70 28=OB:× 28?04:V2
157?5@5G=>W ?>B@518.
5@V>4 3>4C20==O 3@C44N. 52V4><>, G8 ?@>=8:0T 15B03VAB8= C 3@C4=5<>;>; ;N48=8.
>A;V465==O =0 B20@8=0E I>4> ?@>=8:=5==O 15B03VAB8=C 2<>;>;> =5 ?@>2>48;8AL. >@8ABL 2V4
70AB>AC20==O ?@5?0@0BC 4;O <0B5@V A;V4 A?V22V4=>A8B8 7 ?5@52030<8 3>4C20==O 3@C44N
V ?>B5=FW9=8< @878:× 4;O 48B8=8.

VB8.

7207:C 7 =54>AB0B=VABN 40=8E I>4> 157?5:8 B0 5D5:B82=>ABV 70AB>AC20==O 15B03VAB8=C
9>3> =5 @5:><5=4CTBLAO ?@87=0G0B8 4VBO< (2V:× 4> 18 @>:V2).

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

0FVT=B8 7 1@>=EV0;L=>N 0AB<>N, 28@07:>2>N E2>@>1>N H;C=:0 B0 420=04FOB8?0;>W :8H:8 2 0=0
<=57V ?>B@51CNBL @5B5;L=>3> <548G=>3> A?>AB5@565==O ?V4 G0A ;V:C20==O 5ABV=>@<<®.

**40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B× 01> @>1>BV 7
V=H8<8 <5E0=V7<0<8.**

5B03VAB8= ?>:070=89 4;O ;V:C20==O A8=4@>E0@0:B5@87CTBLAO B@V04>N >A=>2=8E A8 AB0=8
<>6CBL =530B82=> 2?;820B8 =0 740B=VABL :5@C20B8 02B>>1V;5< B0 ?@0FN20B8 7 V=H8<8
<5E0=V7<0<8. 0 40=8<8 ;V=VG=8E 4>A;V465=L, I> 282G0;8 2?;82 ?@5?0@0BC =0 740B=VABL
:5@C20B8 02B><>1V;5< V ?@0FN20B8 7 <5E0=V7<0<8, 15B03VAB8= =5 2?;8202 01><02 =5ACBBT289
2?;82 =0 FN 740B=VABL.

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

>A;V465==O in vivo, =0?@02;5=V =0 282G5==O 270T<>4VW 7 V=H8<8 ;V:0@AL:8<8 70A>10<8, =5
?@>2>48;8AO. >3;04C =0 40=V 4>A;V465==O in vitro =5 >GV:CTBLAO ?@83=VG5==O 0:B82=>ABV
D5@<5=BV2 F8B>E@>in vivo.
0=V, >B@8<0=V 2 C<>20E in vitro, A2V4G0BL ?@> ?@83=VG5==O <5B01>;V7 0:B82=VABL<>=>0
:A84078 (), C B><). 5:><5=4CTBLAO 4>B@815@56=>ABV ?@8 >4=>G0A=>AC20==V 15B03VAB8=C B0
V=3V1VB>@V2 (2;;NG0NG8 281V@:>2> ?V4B8?).
A;V;L:8 15B03VAB8= T 0=0;>3× 3VAB0

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

\$0@<0:>48=0

5E0=V7< 4VW 15B03VAB8=C 282G5=89 BV;L:8 G0AB:>2>. A=CT :V;L:0 4>AB>2V@=8E 3V?>B57, I>
?V4B25@46CNBL 40=V 4>A;V465=L =0 B20@8=0E B0 70 CG0ABN ;N459.
?:82 15B03VAB8=C =0 3VAB02AB0=>2;5=>, I> 15B03VAB8= G0AB:>2> ?@>O2;OT 03>=VAB8G=C
0:B82=VABL I>4>1-@5F5?B>@V2, 0 B0:>6 0=B03>=VAB8G=C 0:B82=VABL I>4>3-@5F5?B>@V2 3VAB0
2V9 B:0=8=V B0 ?@>O2;OT =57=0G=C 0:B82=VABL I>4>2-@5F5?B>@V2 3VAB0 71V;LHCT >1 B0
282V;L=5==O 3VAB0 H;OE<< 1;>;C20==O ?@5A8=0?B8G=8E
3-@5F5?B>@V2 B0 V=4C:FVW ?@>F5AC 7=865==O :V;L:>ABV 2V4?>2V4=8E 3-@5F5?B>@V2.
5B03VAB8=<>65 71V;LH8B8 :@>2>BV: C :>E;50@=V9 7>=V, 0 B0:>6 C 2AL>;>2=>:

D0@<0>;>3VG=V 4>A;V465==O =0 B20@8=0E ?@>45<>=AB@C20;8 ?>:@0I5==O :@>2>>1V3C 2
AC48=0E *stria vascularis*2=CB@VH=L>3> 2CE0, <>6;82>, 70 @0EC=>: @>7A;01;5==O ?@5:0?V;O@=8E
ADV=:B5@V2 C A8AB5F8@:C;OFVW 2=CB@VH=L>3> 2CE0. 5B03VAB8= B0:>6 28O282 71V;LH5==O
<>7:>2>3> :@>2>B>;C C ;N48=8.

5B03VAB8= A?@8OT 25AB81C;O@=V9 :> 15B03VAB8= ?@8A:>@NT 2V4=>2;5==O 25AB81C;O@=>W
DC=:FVW ?VA;O >4=>1VG=>W =59@5:B>=V7 H3-@5F5?B>@V2. # ;N459 ?V4 G0A ;V:C20==O
15B03VAB8=× B0:>6 7<5=HC202AO G0A 2V4=>2;5==O 25AB81C;O@=>W DC=:FVW ?VA;O =59@5:B>
5B03VAB8= 7=V2 C 25AB81C;O@=8E O4@0E: 1C;> B0:>6 2AB0=>2;5=>, I> 15B03VAB8=<0T
4>7>70;56=89 V=3VICNG89 2?;82 =0 35=5@0FVN ?V:>28E ?>B5=FV0;V2 C =59@>=0E ;0B5@0;L=8E V
<54V0;L=8E 25AB81C;O@=8E O45@.

\$0@<0>;>48=0ABV 15B03VAB8=C, O: F5 1C;> ?>:070=> =0 B20@8=0E, <>6CBL 70157?5G8B8 ?>78B82=89
B5@0?52B8G=89 5D5:B ?@5?0@0BC C 25AB81C;O@=V9 A8AB5
D5:B82=VABL 15B03VAB8=C ?>:070;8 4>A;V465==O 70 CG0ABN ?0FVT=V2 7 25AB81C;O@=8 70?0
<>@>G5==O< V E2>@>1>N 5=LT@0, ?V4 G0A O:8E A?>AB5@V30;>AO 7<5=H5==O BO6:>ABV B0
G0AB>B8 =0?04V2 70?0<>@>G5==O.

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

A<>:BC20==O

@8 ?5@>@0;L=> V ?@0:B8G=> ?>2=VABN 2A<>:BCTBLAO C B@02=>2V 4C65 =87L:89.

"> D0@<0>.:V=5B8G=V 0=0;V78 ?@>2>4OBLAO H;OE<< 28 :>=F5=B@0FVW <5B01>;VBC
2-?V@848;>FB>2>W :8A;>B8 C ?;072V V A5GV.

@8 ?@89>_{max}) =86G0, =V6 ?@8 ?@89>2=5 CA<>:BC20==O 15B03VAB8=C V45=B8G=5 2 >1>E 28?04:0E,
I> 2:07CT =0 B5, I> ?@89<< W6V ;8H5 C?>2V;L=NT 2A<>:BC20==O ?@5?0@0BC.
>7?>4V;

V4A>B>: 15B03VAB8=C, I> 72O7CTBLAO 7 1V;:0<8 ?;07<8 :@>2V, AB0=>28BL<5=H5 5 %.

V>B@0=AD>@<0FVO

VA;O 2A<>:BC20==O 15B03VAB8= H284:> V<0965 ?>2=VABN<5B01>;V7CTBLAO 2 2-?V@848;>FB>2C
:8A;>BC (O:0 =5 28O2;OT D0@<0>;>3VG=>W 0:B82=>ABV).

VA;O ?@89> :>=F5=B@0FVO 2-?V@848;>FB>2>W :8A;>B8 C ?;072V (B0 2 A5GV) 4>AO30T A2>3>
<0:A848=C ?VA;O ?@89>

82545==O

2-?V@848;>FB>20 :8A;>B0 H284:> 282>48BLAO V7 A5G5N. @8 ?@89>7C20==V 8-48 <3 1;87L:> 85 %
>G0B:>2>W 4>78 28O2;OTBLAO 2 A5GV. 82545==O 15B03VAB8=C =8@:0<8 01> 7 :0;<< T =57=0G=8
V=V9=VABL

(284:VABL 2V4=>2;5==O 70;8H0TBLAO ?>ABV9=>N ?@8 ?5@>@0;L=>

\$0@<0F52B8G=V E0@0:B5@8AB8:8.

A=>2=V DV78:>-EVABV: B01;5B:8 :@C3;>W D>@<8 7 ?>A:>N ?>25@E=5N 7 @8A:>N B0 D0A:>N,
1V;>3> 01> <0965 1V;>3> :>;L>@C. 0 ?>25@E=V B01;5B>: 4>?CA:0TBLAO<0@2VABL(4;O B01;5B>: ?>
8 <3 B0 16 <3).

"5@ABV.3 @>:8.

5 70AB>A>2C20B8 ?@5?0@0B ?VA;O 70:V=G5==O B5@ABV, 2:070=>3> =0 C?0:>2FV.

#<>28 715@V30==O.

15@V30B8 C 70E8I5=> 25 °!.

15@V30B8 C =54>ABC?=>

#?0:>2:0.

> 10 B01;5B>: C 1;VAB5@V. "01;5B:8 ?> 8<3. > 3 1;VAB5@8 C ?0GFV.

"01;5B:8 ?> 16 <3 B0 24 <3. > 3 01> 6 1;VAB5@V2 C ?0GFV.

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

8@>1=8:. " «\$0@<0>».

VAF57=0E>465==O.#:@0W=0, 04080, <. 8W2, 2C;. \$@C=75, 63.

!" #&/
?> <548F8=A:>?@5?0@0B0

!"
(VESTINORM)

!>AB02:

459AB2CNI55 25I5AB2>: betahistine;

1 B01;5B:0 A>45@68B 15B038AB8=0 48384@>E;>@840 8 <3 8;8 16 <3, 8;8 24 <3 2 ?5@5AG5B5 =0 100 %
ACE>5 25I5AB2>;

2A?><>30B5;L=K5 25I5AB20: F5;;N;>70 <8:@>:@8AB0;;8G5A:0O, =0B@8O :@0E<0;3;8;>;OB (B8?), :@5
<=8O 48>:A84 :>;>84=K9 1572>4=K9, ?>284>=, <03=8O AB50@0B.

5:0@AB25==0O D>@<0. "01;5B:8.

\$0@<0:>B5@0?52B8G5c:0O 3@C??0. !@54AB20 4;O ;5G5=8O 25AB81C;O@=KE =0@CH5=89.
>4 "N07! 01.

;8=8G5A:85 E0@0:B5@8AB8:8.

>:070=8O.

>;57=L 8 A8=4@< 5=L5@0, E0@0:B5@87CNI85AO B0:8<8 >A=>2=K<8 A8<0<8:

3>;>2>:@C65=85, A>?@>2>640NI55AO 8=>340 B>H=>B>9 8 @2>B>9;

A=865=85< A;CE0 (BC3>CE>ABLN);

HC<<< 2 CH0E.

!8<0B8G5A:>5 ;5G5=85 25AB81C;O@=>3> 3>;>2>:@C65=8O @07;8G=>3> ?@>8AE>645=8O.

@>B82>?>:070=8O.

8?5@GC2AB28B5;L=>ABL : ;N1>=5=B>2 ?@5?0@0B0. \$5>E@><>F8B><0.

!>A>1 ?@8<5=5=8O 8 4>7K.

07=0G0NB 27@>A;K< 2=CB@L. !CB>G=0O 4>70 A>AB02;O5B 24-48 <3, @02=><5@=>

@0A?@545;5==0O 4;O ?@85<0 =0 ?@>BO65=88 ACB>:.

"01;5B:8 ?> 8 <3	"01;5B:8 ?> 16 <3	"01;5B:8 ?> 24 <3
1-2 B01;5B:8 3 @070 2 ACB:8	½1 B01;5B:0 3 @070 2 ACB:8	1 B01;5B:0 2 @070 2 ACB:8

"01;5B:8 ?@8=8<0NB ?>A;5 54K, =5 @07652K20O.

>7C 8 4;8B5;L=>ABL B5@0?88 >?@545;O5B 2@0G 8=48284C0;L=> 2 7028A8<>AB8 >B

MDD5:B82=>AB8 B5@0?88. #<5=LH5=85 A8<>2 8=>340 =01;N405BAO B>;L:> ?>A;5 2-3 =545;L

;5G5=8O. 08;CGH85 @57C;LB0BK =01;N40NB AO ?@8 ?@8Q<5 ?@5?0@0B0 =0 ?@>BO65=88 =5A:>;L:8E

<5AOF52. A;8 ;5G5=85 =07=0G8BL 2 =0G0;5 701>;520=8O, <>6=> ?@54C?@548BL

?@>3@5AA8@>20=85 53> 8/8;8 ?>B5@N A;CE0 =0 ?>74=8E AB048OE.

0F85=BK ?>68;>3> 2>7@0AB0. >@@@5:F8O 4>7K 4;O ?0F85=B>2 MB>9 3@C??K =5 B@51C5BAO.

>G5G=0O =54>AB0B>G=>ABL. >@@@5:F8O 4>7K =5 B@51C5BAO.

5G5=>G=0O =54>AB0B>G=>ABL. >@@@5:F8O 4>7K =5 B@51C5BAO.

>I>G=K5 @50:F88.

!> AB>@>=K ?8I520@8B5;L=>3> B@0:B0: B>H=>B0, 48A?5?A8O; 60;>1K =0 =57=0G8B5;L=K5

@0AAB@>9AB20 65;C4:0 (@2>B0, 1>;L 2 682>B5, 274CB85 682>B0 8 <5B5>@87<). -B8 ?>1>G=K5

MDD5:BK >1KG=> 8AG570NB ?@8 ?@85<5 ?@5?0@0B0 A ?8I59 8;8 ?>A;5 C<5=LH5=8O 4>7K.

!> AB>@>=K =5@2=>9 A8AB53>;>2=0O 1>;L.

!> AB>@>=K 8<9 A8AB5 @50:F88 38?5@GC2AB28B5;L=>AB8, =0?@8<5@ 0=0D8;0:A8O.
!> AB>@>=K :>68 8 ?>4:>6=>9 :;5BG0B:8: @50:F88 38?5@GC2AB28B5;L=>AB8 :>68 8 ?>4:>6=>9
68@>2>9 :;5BG0B:8, 2 G0AB=>AB8 0=38=>52@>B8G5A:89 >B5.; AK?L, 7C4 8 :@0?82=8F0.

5@54>78@>2:0.

725AB=>=5A:>;L:> A;CG052 ?5@54>78@>2:8 15B038AB8=0. # =5:>B>@KE ?0F85=B>2 =01;N40;8AL ;53:
85 8 C<5@5==K5 A8<K (B>H=>B0, A>=;82>ABL, 1>;L 2 682>B5) ?>A;5 ?@85<0 15B038AB8=0 2 4>70E
4> 640 <3. >;55 A5@L57=K5 >A;>6=5=8O (AC4>@>38, A5@45G=>-;53>G=K5 >A;>6=5=8O) =01;N40;8AL
?@8 ?@54=0<5@5==>< ?@85<5 ?>2KH5==KE 4>7 15B038AB8=0, >A>15==> 2 A>G5B0=88 A ?5@54>7
8@>2:>9 4@C38E ;5:0@AB25==KE A@54AB2.
5G5=85 ?5@54>78@>2:8
5G5=85 ?5@54>78@>2:8 4>;6=> 2;;NG0BL AB0=40@B=K5 ?>445@6820NI85 <5@K.

@8<5=5=85 2 ?5@8>4 15@5<5==>AB8 8;8 :>@<;5=8O 3@C4LN.

5@5<5==>ABL. 5B 4>AB0B>G=KE 40==KE ?> ?@8<5=5=8N 15B038AB8=0 15@5<5==K< 65=I8=0<.
57C;LB0BK 8AA;54>20=89 =0 682>B=KE O2;ONBAO =54>AB0B>G=K<8 4;O >F5=:8 2;8O=8O =0
B5G5=85 15@5<5==>AB8, @0728B85 M<1@8>=0/?;>40, @>4K 8 ?>AB=0B0;L=>5 @0728B85. >B5=F
80;L=K9 @8A: 4;O G5;>25:0 =58725AB5=. 5B038AB8= =5 A;54C5B ?@8<5=OBL 2 ?5@8>4 15@5
<5==>AB8, 70 8A;;NG5=85< A;CG052 =5?@>25@68<>9 =5>1E>48<>AB8.
5@8>4 :>@<;5=8O 3@C4LN. 58725AB=>, ?@>=8:05B ;8 15B038AB8= 2 3@C4=>5 <>;> G5;>25:0.
AA;54>20=8O =0 682>B=KE ?> ?@>=8:=>25=8N 15B038AB8=0 2 <>;> =5 ?@>2>48;8AL. >;L7C ?@8
?@8<5=5=8O ?@5?0@0B0 4;O <0B5@8 A;54C5B A>>B=>A8BL A ?@58 :>@<;5=8O 3@C4LN 8 ?>B5=F
80;L=K< @8A:>< 4;O @515=:0.

5B8.

A2O78 A =54>AB0B>G=>ABLN 40==KE ?> 157>?0A=>AB8 8 MDD5:B82=>AB8 ?@8<5=5=8O 15B038
AB8=0 53> =5 @5:><5=4C5BAO =07=0G0BL 45BO< (4> 18 ;5B).

A>15==>AB8 ?@8<5=5=8O.

0F85=BK A 1@>=E80;L=>9 0AB<>9, O725==>9 1>;57=LN 65;C4:0 8 425=04F0B8?5@AB=>9 :8H:8 2 0=0
<=575 B@51CNB BI0B5;L=>3> <548F8=A:>3> =01;N45=8O 2> 2@5@<>

**!>A>1=>ABL 2;8OBL =0 A:>@>ABL @50:F88 ?@8 C?@02;5=88 02B>B@0=A?>@B< 8;8 @01>B5 A
4@C38<8 <5E0=87<0<8.**

5B038AB8= ?>:070= 4;O ;5G5=8O A8=4@<0 5=L5@0, :>B>@K9 E0@0:B5@87C5BAO B@804>9 >A=>2=
KE A8<>2: 3>;>2>:@C65=85<, A=865=85< A;CE0, HC<>< 2 CH0E, 0 B0:65 4;O A8<0B8G5A:>3> ;5G5=8O
25AB81C;O@=>3> 3>;>2>:@C65=8O. 10 A>AB>O=8O <>3CB =530B82=> 2;8OBL =0 A?>A>1=>ABL
C?@02;OBL 02B><>18;5< 8 @01>B0BL A 4@C38<8 <5E0=87<0<8. > 40==K< :;8=8G5A:8E 8AA;54>20=89
, :>B>@K5 87CG0;8 2;8O=85 ?@5?0@0B0 =0 A?>A>1=>ABL C?@02;OBL 02B><>18;5< 8 @01>B0BL A
<5E0=87<0<8, 15B038AB8= =5 2;8O; 8;8>:07K20; =5ACI5AB25==>5 2;8O=85 =0 MBC A?>A>1=>ABL.

708<>459AB285 A 4@C38<8 ;5:0@AB25==K<8 A@54AB20<8 8 4@C385 284K 2708<>459AB289.

AA;54>20=8O in vivo, =0?@02;5==K5 =0 87CG5=85 2708<>459AB28O A 4@C38<8 ;5:0@AB25==K<8
A@54AB20<8, =5 ?@>2>48;8AL. 0 >A=>25 40==KE 8AA;54>20=8O in vitro =5 >68405BAO C3=5B5=8O
0:B82=>AB8 D5@<5=B>2 F8B>E@><0 P450 in vivo.
0==K5, ?>;CG5==K5 2 CA;>28OE in vitro, A2845B5;LAB2CNB >1 C3=5B5=88 <5B01>;87<0 15B038AB8=0
?@5?0@0B0<8, :>B>@K5 8=3818@CNB 0:B82=>ABL <>=>0<8=>>:A8407K (), 2 B>< G8A;5 ?>4B8?
(=0?@8<5@ A5;538;8=>). 5:><5=4C5BAO A>1;N40BL >AB>@>6=>ABL ?@8 >4=>2@5<5==>< ?@8
<5=5=88 15B038AB8=0 8 8=3818B>@>2 (2;;NG0O 8718@0B5;L=> ?>4B8?).
>A:>;L:C 15B038AB8= O2;O5BAO 0=0;>3>< 38AB0<8=0, 2708<>459AB285 15B038AB8=0 A 0=B838AB0
<8==K<8 ?@5?0@0B0<8 <>65B B5>@5B8G5A:8 ?>2;8OBL =0 MDD5:B82=>ABL >4=>3> 87 MB8E
?@5?0@0B>2.

\$0@<0:>;>38G5A:85 A2>9AB20.

\$0@<0:>48=0<8:0.

5E0=87< 459AB28O 15B038AB8=0 87CG5= B>;L:> G0AB8G=>. !CI5AB2C5B =5A:>;L:> 4>AB>25@=KE 38?>B57, ?>4B25@640NI8E 40==K5 8AA;54>20=89 =0 682>B=KE 8 ?@8 CG0AB88 ;N459.

:8O=85 15B038AB8=0 =0 38AB0<8=5@38G5A:CN A8AB5 CAB0=>2;5=>, GB> 15B038AB8= G0AB8G=> ?@>O2;O5B 03>=8AB8G5A:CN 0:B82=>ABL >B=>A8B5;L=> 1-@5F5?B>@>2, 0 B0:65

0=B03>=8AB8G5A:CN 0:B82=>ABL >B=>A8B5;L=> 3-@5F5?B>@>2 38AB0<8=0 2 =5@2=>9 B:0=8 8 ?@>O2;O5B =57=0G8B5;L=CN 0:B82=>ABL >B=>A8B5;L=> 2-@5F5?B>@>2 38AB0<8=0. 5B038AB8=

C25;8G8205B >1<5= 8 2KA2>1>645=85 38AB0<8=0 ?CB5< 1;>;8@>20=8O ?@5A8=0?B8G5A:8E 3- @5F5?B>@>2 8 8=4C:F88 ?@>F5AA0 A=865=8O :>;8G5AB20 A>>B25BAB2CNI8E 3-@5F5?B>@>2.

5B038AB8= <>65B C25;8G8BL :@>2>B>: 2 :>E;50@=>9 7>=5, 0 B0:65 2> 2A5< 3>;>2=<< <>735: D0@ <0:>;>38G5A:85 8AA;54>20=8O =0 682>B=KE ?@>45<>=AB@8@>20;8 C;CGH5=85 :@>2>>1@0I5=8O 2

A>AC40E *stria vascularis*2=CB@5==53> CE0, 2>7<>6=>, 70 AG5B @0AA;01;5=8O ?@5:0?8;;O@=KE AD8=:B5@>2 2 A8AB5<5 <8:@>F8@:C;OF88 2=CB@5==53> CE0. 5B038AB8= B0:65 ?@>45

<>=AB@8@>20; C25;8G5=85 <>73>2>3> :@>2>B>:0 C G5;>25:0. 5B038AB8= A?>A>1AB2C5B 25AB81C;O@=>9 :>: 15B038AB8= CA:>@O5B 2>AAB0=>2;5=85

25AB81C;O@=>9 DC=:F88 ?>A;5 >4=>AB>@>==59 =59@M:B><88 C 682>B=KE, CA:>@OO 8 A?>A>1AB2CO F5=B@0;L=>9 25AB81C;O@=>9 :>B MDD5:B E0@0:B5@87C5BAO CA8;5=85<

@53C;OF88 >1<5=0 8 2KA2>1>645=8O 38AB0<8=0 8 @50;87C5BAO 2 @57C;LB0B5 0=B03>=87<0 H3- @5F5?B>@>2. # ;N459 2> 2@5< B0:65 C<5=LH0;>AL 2@5AAB0=>2;5=8O 25AB81C;O@=>9 DC=:F88 ?>A;5 =59@M:B><88.

5B038AB8= 87<5=O5B 0:B82=>ABL =59@>=>2 2 25AB81C;O@=KE O4@0E: 1K;> B0:65 CAB0=>2;5=>, GB> 15B038AB8= 8<55B 4>7>7028A8<>5 8=3818@CNI55 2;8O=85 =0 35=5@0F8N ?8:>2KE ?>B5=F80;>2 2 =59@>=0E ;0B5@0;L=KE 8 <5480;L=KE 25AB81C;O@=KE O45@.

\$0@<0:>48=0<8G5A:85 A2>9AB20 15B038AB8=0, :0: MB> 1K;> ?>:070=> =0 682>B=KE, <>3CB >15A?5G8BL ?>;>68B5;L=K9 B5@0?52B8G5A:89 MDD5:B ?@5?0@0B0 2 25AB81C;O@=>9 A8AB5<5.

-DD5:B82=>ABL 15B038AB8=0 ?>:070;8 8AA;54>20=8O A CG0AB85< ?0F85=B>2 A 25AB81C;O@=K< 3>;>2>:@C65=85< 8 1>;57=LN 5=L5@0, 2> 2@5B>@KE =01;N40;>AL C<5=LH5=85 BO65AB8 8 G0AB>BK ?@8ABC?>2 3>;>2>:@C65=8O.

\$0@<0:>:8=5B8:0. A0AK20=85

@8 ?5@>@0;L=<< 22545=88 15B038AB8= 1KAB@> 8 ?@0:B8G5A:8 ?>;=>ABLN 2A0AK205BAO 2 ?8I520@8B5;L=<< B@0:B5. >A;5 2A0AK20=8O ?@5?0@0B 1KAB@> 8 ?>GB8 ?>;=>ABLN <5B01>;878@C5BAO A >1@07>20=85< <5B01>;8B0 2-?8@848;C:ACA=>9 :8A;>BK. #@>25=L :=F5=B@0F88 15B038AB8=0 2 ?;07<5 :@>28 >G5=L =87:89.

>MB> @8 ?@85<5 ?@5?0@0B0 A ?8I59 <0:A8<0;L=0O 53> :=F5=B@0F8O (C_{max}) =865, G5< ?@8 ?@85<5 =0B>I0:. @8 MB<< ?>;=>5 2A0AK20=85 15B038AB8=0 845=B8G=> 2 >1>8E A;CG0OE, GB> C:07K205B =0 B>, GB> ?@85< ?8I8 B>;L:> 70<54;O5B 2A0AK20=85 ?@5?0@0B0.

0A?@545;5=85 @>F5=B 15B038AB8=0, :>B>@K9 A2O7K205BAO A 15;:0<8 ?;0728, A>AB02;O5B <5=LH5 5 %. 8>B@0=AD>@<0F8O

>A;5 2A0AK20=8O 15B038AB8= 1KAB@> 8 ?>GB8 ?>;=>ABLN <5B01>;878@C5BAO 2 2- ?8@848;C:ACA=CN :8A;>BC (:>B>@0O =5 ?@>O2;O5B D0@<0:>;>38G5A:>9 0:B82=>AB8).

>A;5 ?@85<0 15B038AB8=0 2=CB@L :=F5=B@0F8O 2-?8@848;C:ACA=>9 :8A;>BK 2 ?;07<5 :@>28 (8 2 <>G5) 4>AB8305B A2>53> <0:A8

K2545=85 2-?8@848;C:ACA=0O :8A;>B0 1KAB@> 2K2>48BAO A <>G>9. @8 ?@85<5 ?@5?0@0B0 2 4>78@>2:5 8- 48 <3 >:>;> 85 % =0G0;L=>9 4>7K >1=0@C68205BAO 2 <>G5. K2545=85 15B038AB8=0 ?>G:0<8 8;8 A :0;> < O2;O5BAO =57=0G8B5;L=K

8=59=>ABL !:>@>ABL 2>AAB0=>2;5=8O >AB05BAO ?>AB>O==>9 ?@8 ?5@>@0;L=<< ?@85<5 8-48 <3 ?@5?0@0B0, GB> C:07K205B =0 ;8=59=>ABL D0@<0:>:8=5B8:8 15B038AB8=0 8 405B 2>7<>6=>ABL ?@54?>;>68BL, GB> 70459AB2>20==K9 <5B01>;8G5A:89 ?CBL O2;O5BAO =5=0AKI5==K<.

\$0@<0F52B8G5A:85 E0@0:B5@8AB8:8.

A=>2=K5 D878:-E8<8G5A:85 A2>9AB20: B01;5B:8 :@C3;>9 D>@A:>9 ?>25@E=>ABLN A @8A:>9 8
D0A:>9, 15;>3> 8;8 ?>GB8 15;>3> F25B0. 0 ?>25@E=>AB8 B01;5B>: 4>?CA:05BAO <@0<>@=>ABL (4;O
B01;5B>: ?> 8 <3 8 16 <3).

!@>: 3>4=>AB8. 3 3>40.

5 ?@8<5=OBL ?@5?0@0B ?>A;5 >:=G0=8O A@>:0 3>4=>AB8, C:070==>3> =0 C?0:>2:5.

#A;>280 E@0=5=80.

%@0=8BL 2 70I8I5==<>B A25B0 <5AB5 ?@8 B5

%@0=8BL 2 =54>ABC?=<> 4;O 45B59 <5AB5.

#?0:>2:0.

> 10 B01;5B>: 2 1;8AB5@5. "01;5B:8 ?> 8 <3. > 3 1;8AB5@0 2 ?0G:5.

"01;5B:8 ?> 16 <3 8 24 <3. > 3 8;8 6 1;8AB5@>2 2 ?0G:5.

0B53>@8O >B?CA:0. > @5F5?BC.

@>872>48B5;L.

<<\$0@<0:>».

5AB>=0E>645=85.

#: @08=0, 04080, 3. 852, C;. \$@C=75, 63.