

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

"!®
(BETASERC®)

!;:04:

4VNG0 @5G>28=0: 15B03VAB8=C 483V4@>E;>@84;

1 B01;5B:0 E;>@84C 8, 16 01> 24 <3;

4>?>28=8: F5;N;>70 :@8AB0;VG=0, <0=VB (421), :8A;>B8 ;8<=>W <=>3V4@0B, :@5<=VN 4V>:A84
:>;>W4=89 1572>4=89, B0;L:.

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

A=>2=V DV78:>-EVABV:

B01;5B:8 ?> 8 <3: :@C3;V, ?;>A:V, 1V;V 01<0965 1V;V B01;5B:8 7V A:>H5=8<8 :@0O<8, 7 <0@:C20==O
< «256» 7 >4=>3> 1>:C B01;5B:8;

B01;5B:8 ?> 16 <3: :@C3;V, 42>>?C:;V, 4V;8<0965 1V;V B01;5B:8 7V A:>H5=8<8 :@0O<8, 7 >4=>3> 1>:C 7
=0AVG:>N V <0@:C20==O< «267» ?> >18420 1>:8 2V4 =0AVG:8; B01;5B:C <>6=0 @>74V;8B8 =0 42V
@V2=V 4>78;

B01;5B:8 ?> 24 <3: :@C3;V, 42>>?C:;V, 4V;8<0965 1V;V B01;5B:8 7V A:>H5=8<8 :@0O<8, 7 >4=>3> 1>:C 7
=0AVG:>N V <0@:C20==O< «289» ?> >18420 1>:8 2V4 =0AVG:8; =0AVG:0 ?@87=0G5=0 BV;L:8 4;O
?>;53H5==O @>7;0

\$0@<0:>B5@0?52B8G=0 3@C?0. 0A>18 4;O ;V:C20==O 25AB81C;O@=8E ?>@CH5=L.
>4 "X N07C A01.

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

\$0@<0:>48=0

5E0=V7< 4VW 15B03VAB8=C 282G5=89 ;8H5 G0AB:>2>. A=CT 45;V;L:0 4>AB>2V@=8E 3V?>B57, O:V
1C;8 ?V4B25@465=V 40=8<8 4>A;V465=L, ?@>2545=8<8 =0 B20@8=0E B0 70 CG0ABN ;N459.

?;82 15B03VAB8=C =0 3VAB0

AB0=>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 3VAB02V9 B:0=8=V B0 <0T =57=0G=C
0:B82=VABL I>4>2-@5F5?B>@V2 3VAB01 <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;LHC20B8 :@>2>BV: 2 :>E;50@=V9 7>=V, 0 B0:>6 C 2AL>;>2=>.

\$0@<0:>;>3VG=V 4>A;V465==O =0 B20@8=0E ?@>45<=>AB@C20;8 ?>:@015==O :@>2>>1V3C 2
AC48=0E stria vascularis2=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 ?@>45<=>AB@C202
71V;LH5==O <>7:>2>3> :@>2>B>:C 2 >@30=V7

5B03VAB8= A?@8OT 25AB81C;O@=V9 :>.

5B03VAB8= ?@8A:>@NT 2V4=>2;5==O 25AB81C;O@=>W DC=:FVW ?VA;O >4=>1VG=>W =59@5:B>
F5AC F5=B@0;L=>W 25AB81C;O@=>W :>A8;5==O< @53C;OFVW >1=V7H3-@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.

C;> B0:>6 2AB0=>2;5=>, I> 15B03VAB8=<0T 4>7>70;56=89 V=3V1CNG89 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=> C B20@8=, <>6CBL 70157?5G8B8 ?>78B82=89

B5@0?52B8G=89 5D5:B ?@5?0@0BC 2 25AB81C;O@=V9 A8AB5

D5:B82=VABL 15B03VAB8=C 1C;0 ?>:070=0 ?V4 G0A 4>A;V465=L C ?0FVT=V2 7 25AB81C;O@=8
70?0<>@>G5==O< B0 E2>@>1>N 5=LT@0, I> 1C;> ?@>45<=>AB@>20=> H;OE<< 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 2 CAVE 2V44V;0E H;C=>2>-.8H:>2>3> B@0:BC. VA;O 2A<>:BC20==O ?@5?0@0B H284:> V <0965 ?>2=VABN<5B01>;V7CTBLAO 7 CB2>@5==O< <5B01>;VBC 2-?V@848;>FB>2>W :8A;>B8. V25=L :>F5=B@0FVW 15B03VAB8=C C ?;07 2V 4C65 =87L:89. ">=F5=B@0FVW <5B01>;VBC 2-?V@848;>FB>2>W :8A;>B8 C ?;07 @8 ?@89>max) ?@5?0@0BC =86G0, =V6 ?@8 ?@89>2=5 2A<>: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 ?@>F5A 2A<>:BC20==O ?@5?0@0BC.

>7?>4V;.

V4A>B>: 15B03VAB8=C, I> 7207CTBLAO 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 <0T D0@<0:>;>3VG=>W 0:B82=>ABV).

VA;O ?@89>=F5=B@0FVO 2-?V@848;>FB>2>W :8A;>B8 2 ?;072V (B0 2 A5GV) 4>AO30T A2>3><0:A8 48=C ?VA;O ?@89>

82545==O.

2-?V@848;>FB>20 :8A;>B0 H284:> 282>48BLAO 7 A5G5N. @8 ?@89>7C20==V 848 <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=> 48 <3 ?@5?0@0BC, 2:07CNG8 =0 ;V=V9=VABL D0@<0:>:V=5B8:8 15B03VAB8=C, V 40T<>6;82VABL ?@8?CAB8B8, I> 704VO=89 <5B01>;VG=89 H;OE T =5=0A8GC20=8

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

>:070==O.

%2>@>10 V A8=4@< 5=LT@0, O:V E0@0:B5@87CNBLAO B@L<0 >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.

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

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

V4 G0A ;V:C20==O ?@5?0@0B< =5>1EV4=> @5B5;L=> :>=B@>;N20B8 AB0= ?0FVT=BV2 7 1@>=EV0;L=>N 0AB<>N B0/01> 28@07:>2>N E2>@>1>N H;C=:0 B0 420=04FOB8?0;>W :8H:8 2 0=0 <=57V.

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=FV9=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=V9=8< @878:>< 4;O 48B8=8.

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.

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.

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

>1>20 4>70 4;O 4>@>A;8E 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
12 B01;5B:8 3 @078 =0 4>1C	1/2 B01;5B:0 3 @078 =0 4>1C	1 B01;5B:0 2 @078 =0 4>1C

>7C A;V4 ?V418@0B8 V=482V4C0;L=>, 70;56=> 2V4 5D5:BC. <5=H5==O A8;8 A?>AB5@V30TBLAO
 BV;L:8 ?VA;O 42>E-B@L>E B86=V2 ;V:C20==O. 09:@0IV @57C;LB0B8 V=:>;8 4>AO30NBLAO ?@8
 ?@89>BO3<< :V;L:>E B5, I> ?@87=0G5==O ;V:C20==O =0 ?>G0B:C 70E2>@N20==O 70?>1V30T 9>3>
 ?@>3@5AC20==N V/01> 2B@0BV A;CEC =0 ?V7=VE AB04VOE.

0FVT=B8 ;VB=L>3> 2V:C

%>G0 =0 AL>3>4=V 40=V ;;V=VG=8E 4>A;V465=L C FV9 3@C?V ?0FVT=V2 >1<565=V, H8@>:89
 4>A2V4 70AB>AC20==O ?@5?0@0BC C ?VA;O@5TAB@0FV9=>4V ?@8?CA:0T, I> :>@5:FVO 4>78 4;O
 FVTW ?>?C;OFVW ?0FVT=V2 =5 ?>B@V1=0.

8@>:20 =54>AB0B=VABL

FV9 3@C?V ?0FVT=V2 A?5FV0;L=V ;;V=VG=V 28?@>1C20==O =5 ?@>2>48;8AO, 0;5 2V4?>2V4=>
 4> 4>A2V4C ?VA;O@5TAB@0FV9=>3> 70AB>AC20==O :>@5:FVO 4>78 =5 ?>B@V1=0.

5GV=:>20 =54>AB0B=VABL

FV9 3@C?V ?0FVT=V2 A?5FV0;L=V ;;V=VG=V 28?@>1C20==O =5 ?@>2>48;8AO, 0;5 2V4?>2V4=>
 4> 4>A2V4C ?VA;O@5TAB@0FV9=>3> 70AB>AC20==O :>@5:FVO 4>78 =5 ?>B@V1=0.

VB8.

7207:C 7 =54>AB0B=VABN 40=8E I>4> 157?5:8 B0 5D5:B82=>ABV 70AB>AC20==O ?@5?0@0BC
 5B0A5@:® 9>3> =5 @5:><5=4CTBLAO ?@87=0G0B8 4VBO< (2V:<< 4> 18 @>:V2).

5@54>7C20==O.

V4><> :V;L:0 28?04:V2 ?5@54>7C20==O ?@5?0@0BC. # 45O:8E ?0FVT=V2 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.

>1VG=V @50:FVW.

86G5707=0G5=V ?>1VG=V @50:FVW A?>AB5@V30;8AO C ?0FVT=V2, O:V 70AB>A>2C20;8 5B0A5@:
 ® ?V4 G0A ?;0F51>-:>=B@>;L>20=8E 4>A;V465=L, 7 B0:>N G0AB>B>N: 4C65 G0ABV (≥ 1/10), G0ABV
 (2V4 ≥ 1/100 4> <1/10), =5G0ABV (2V4 ≥ 1/1000 4> <1/100), ?>>48=>:V (2V4 ≥ 1/10000 4> <1/1000),
 @V4:VA=V (<1/10000).

I>:C H:C=:>2>-:8H:>2>3> B@0:BC

'0ABV: =C4>B0 B0 48A?5?AVO.

I>:C =5@2>2>W A8AB5<8

'0ABV: 3>;>2=89 1V;L.

0 4>40B>: 4> 28?04:V2, ?@> O:V ?>2V4<<;O;>AO ?V4 G0A ;;V=VG=8E 4>A;V465=L, ?@>
=86G5707=0G5=V =51060=V O28I0 ?>2V4<<;O;>AO A?>=B0==> C E>4V ?>AB<0@:5B8=3>2>3>
70AB>AC20==O B0 2V4><> 7 =0C:>2>W ;VB5@0BC@8. 0 =0O2=8<8 40=8<8 G0AB>BC =5 <>6=0
2AB0=>28B8, B=>0 ;;0A8DV:>20=0 O: =52V4<<0.

I>:C VW A8AB5<8

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

I>:C H;C=:>2>-.8H:>2>3> B@0:BC

!:@38 =0 =57=0G=V @>7;048 H;C=:0 (1;N20==O, 30AB@>V=B5AB8=0;L=89 1V;L, 74CBBO 682>B0 B0
<5B5>@87<). &V ?>1VG=V 5D5:B8 70728G09 7=8:0NBL ?@8 ?@89>7 W65N 01> ?VA;O 7<5=H5==O
4>78.

I>:C H:V@8 V?V4H:V@=>W ;:VB:>28=8

!>AB5@V30;8AO @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@ABV.5 @>:V2.

#<>28 715@V30==O. 15@V30B8 2 >@83V=0;L=V9 C?0:>2FV ?@8 B5ABC?=>.

#?0:>2:0.

"01;5B:8 ?> 8 <3: ?> 15 B01;5B>: C 1;VAB5@V, ?> 2 1;VAB5@8 2 :0@B>==V9 C?0:>2FV; ?> 30 B01;5B>: C
1;VAB5@V, ?> 1 1;VAB5@C 2 :0@B>==V9 C?0:>2FV; ?> 25 B01;5B>: C 1;VAB5@V, ?> 4 1;VAB5@8 2
:0@B>==V9 C?0:>2FV;

B01;5B:8 ?> 16 <3: ?> 15 01> 21 B01;5BFV C 1;VAB5@V, ?> 2 1;VAB5@8 2 :0@B>==V9 C?0:>2FV; ?> 20
B01;5B>: C 1;VAB5@V, ?> 3 1;VAB5@8 2 :0@B>==V9 C?0:>2FV;

B01;5B:8 ?> 24 <3: ?> 10 B01;5B>: C 1;VAB5@V, ?>1 01> 5 1;VAB5@V2C :0@B>==V9 C?0:>2FV; ?> 20
B01;5B>: C 1;VAB5@V, ?> 1, 3 01> 5 1;VAB5@V2C :0@B>==V9 C?0:>2FV; ?> 25 B01;5B>: C 1;VAB5@V,
?> 2 01> 4 1;VAB5@8 2 :0@B>==V9 C?0:>2FV.

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

8@>1=8:.

11>BB %5;A:50 !!, \$@0=FVO/Abbott Healthcare SAS, France.

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

CB 45 5;L2V;L, L9> 4V 5;0@, 01400, (0B89>=-AN@-(0;0@>=, \$@0=FVO/Route de Belleville, Lieu dit
Maillard, 01400, Chatillon-sur-Chalaronne, France.