**Supplementary material A**

. nstagebin, accrate(300 300 300 300 300) arms(3 3 3 3 3) theta0(0.07) theta1(0) ctrlp(0.837) alpha(0.5 .3 0.2 .1 .025) power(0.9 0.9

> .95 .95 .95) fu(0) ltfu(0) aratio(1) extrat(0) nstage(5) tunit(1) ess probs

n-stage trial design version 1.0.1, 17 Jul 2014

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Sample size for a 3-arm 5-stage trial with binary outcome based

on Bratton et al. (2013) BMC Med Res Meth 13:139

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Control arm event rate = 0.84

Operating characteristics

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Alpha(1S) Power theta|H0 theta|H1 Length\* Time\*

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Stage 1 0.5000 0.900 0.070 0.000 0.910 0.910

Stage 2 0.3000 0.900 0.070 0.000 0.910 1.820

Stage 3 0.2000 0.950 0.070 0.000 1.620 3.440

Stage 4 0.1000 0.950 0.070 0.000 1.330 4.770

Stage 5 0.0250 0.950 0.070 0.000 2.470 7.240

Pairwise 0.0148 0.802 7.240

FWER (SE) 0.0277 (0.0003)

----------------------------------------------------------------------

\* Length (duration of each stage) is expressed in year periods

Cumulative sample sizes per arm per stage

---------Stage 1--------- ---------Stage 2---------

Overall Control Exper. Overall Control Exper.

---------------------------------------------------------------------------

Number of active arms 3 1 2 3 1 2

Accrual rate\* 300.0 100.0 200.0 300.0 100.0 200.0

Active arms

Patients for analysis 273 91 91 546 182 182

Patients recruited\*\* 273 91 91 546 182 182

All arms

Patients recruited\*\* 273 546

---------------------------------------------------------------------------

---------Stage 3--------- ---------Stage 4---------

Overall Control Exper. Overall Control Exper.

---------------------------------------------------------------------------

Number of active arms 3 1 2 3 1 2

Accrual rate\* 300.0 100.0 200.0 300.0 100.0 200.0

Active arms

Patients for analysis 1032 344 344 1431 477 477

Patients recruited\*\* 1032 344 344 1431 477 477

All arms

Patients recruited\*\* 1032 1431

---------------------------------------------------------------------------

---------Stage 5---------

Overall Control Exper.

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Number of active arms 3 1 2

Accrual rate\* 300.0 100.0 200.0

Active arms

Patients for analysis 2172 724 724

Patients recruited\*\* 2172 724 724

All arms

Patients recruited\*\* 2172

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\* Accrual rates are specified in number of patients per year

\*\* Accounts for loss-to-follow-up rate and includes those recruited during follow-up periods

Expected sample size | 0 effective arms = 690

Expected sample size | 2 effective arms = 1928

Prob. of k experimental arms passing each stage: 0 effective arms

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k(# arms) 0 1 2

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Stage 1 0.332 0.334 0.334

Stage 2 0.611 0.267 0.122

Stage 3 0.785 0.169 0.045

Stage 4 0.892 0.092 0.016

Stage 5 0.972 0.026 0.002

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Prob. of k experimental arms passing each stage: 2 effective arms

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k(# arms) 0 1 2

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Stage 1 0.033 0.136 0.832

Stage 2 0.057 0.189 0.754

Stage 3 0.066 0.205 0.729

Stage 4 0.073 0.218 0.709

Stage 5 0.081 0.232 0.687