BRITISH AMERICAN TOBACCO

Clinical Studies: The influence of Reduced Toxicant Prototype cigarettes on biomarkers of exposure and biological effect in smokers

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Outline

- Context
- Clinical study 1 - completed
  - Products
  - Design
  - Results and Conclusions
- Clinical study 2 - planned
  - Rationale
  - Design
  - Endpoints and Status

Context

- The Institute of Medicine (IoM): *Clearing the Smoke: assessing the science base for tobacco harm reduction* (Stratton *et al*., 2001)
  - Proposed the development of potential reduced-exposure products (PREPs) as a possible way to reduce the harm caused by tobacco use.
  - Defined a PREP as a product that

    (1) results in the substantial reduction in exposure to one or more tobacco toxicants and

    (2) can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects”

- Clinical Study 1 addresses (1):
  - Are cigarettes with substantially reduced levels of tobacco smoke toxicants also associated with reduced toxicant exposure compared with conventional cigarettes?
  - Evaluation of **biomarkers of exposure (BoE)** to toxicants in smokers switched from conventional cigarettes to cigarettes with reduced levels of certain smoke toxicants.

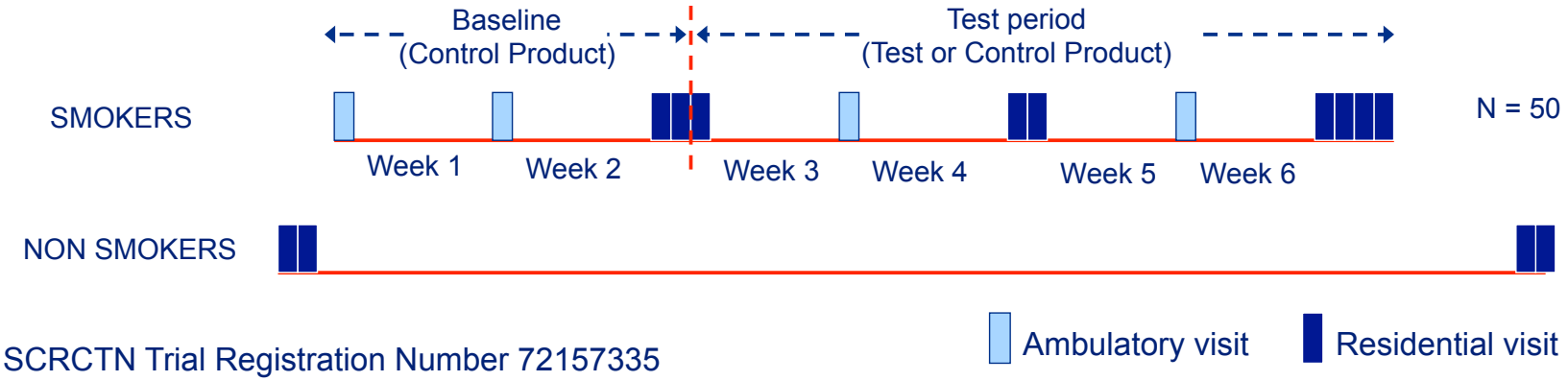
Clinical Study 1 - Products

Product	Tobacco blend	Cigarette filter	ISO* tar yield target (actual)	HCI# tar yield
CC6	100% US style	Mono: Cellulose acetate (CA)	6mg (5.0mg)	24.4mg

- CC – control cigarette (German market based)
- TSS – tobacco sheet substitute (dilutes smoke)
- BT – blend treated tobacco (removes toxicant precursors)
- Carbon – high activity carbon (selectively adsorbs vapour phase smoke toxicants)
- Resin - amine-functionalised resin (reduces additional acidic and carbonyl vapour phase toxicants)

Clinical Study 1 - Design

- Six week single-centre, single-blinded, randomised controlled switching study with occasional clinical confinement*
  - Conducted at Momentum Pharma Sevices, Hamburg and approved by local Ethics
  - Two week baseline period followed by 4 week test period
- Recruited 300 healthy adult subjects
  - 100 smokers of 6-7mg ISO tar yield cigarettes (assigned to the 6mg groups)
    - 50 remain on control (CC6) and 50 switch to test product (TSS6)
  - 150 smokers of 1-2 mg ISO tar yield cigarettes (assigned to the 1mg groups)
    - 50 remain on control (CC1), 50 switched to test product 1 (TSS1) and 50 switched to test product 2 (BT1)
  - 50 non smokers



* ISCRCTN Trial Registration Number 72157335

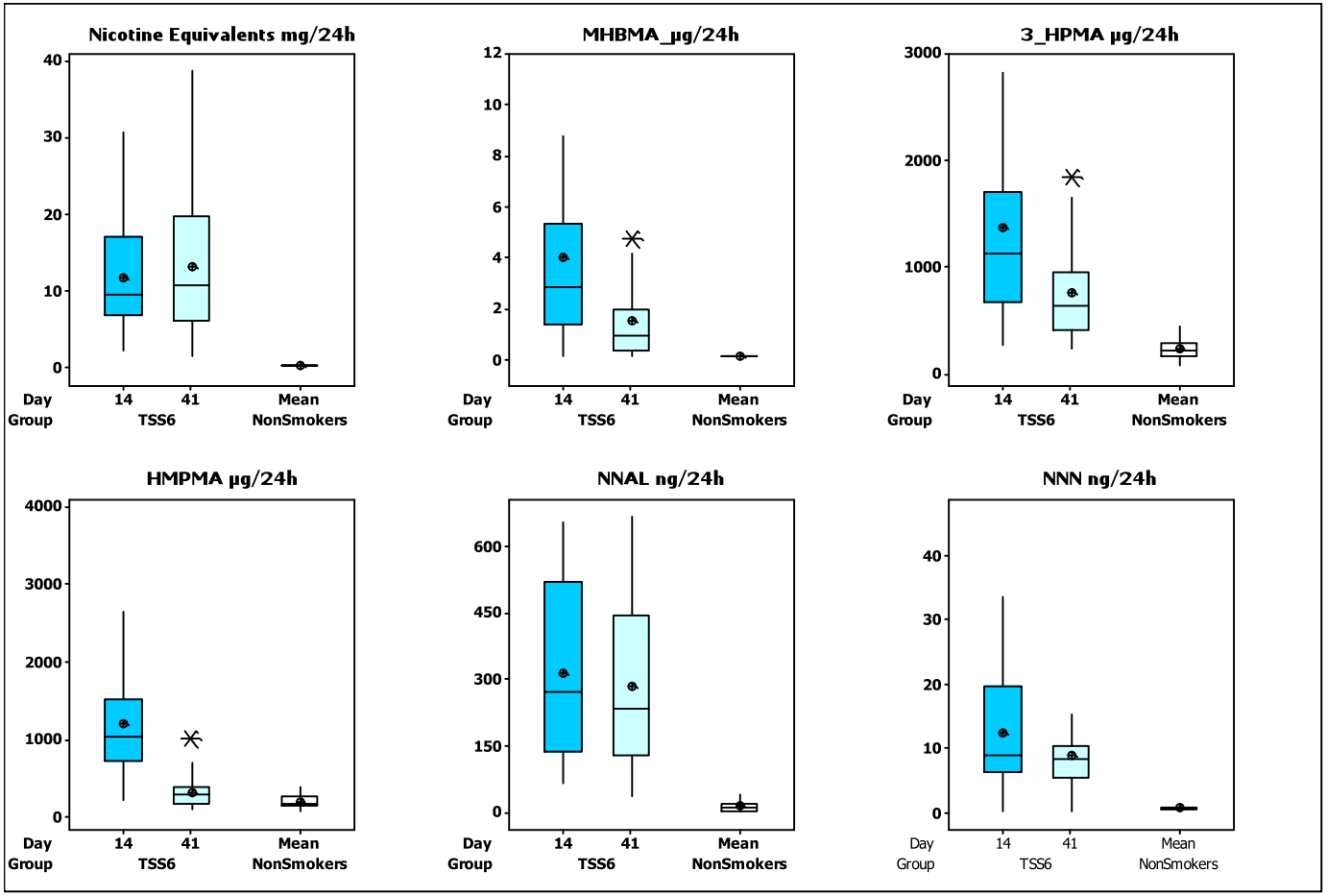
Clinical Study 1 Results

- Prototype cigarette smoke toxicants were generally lower or substantially lower (10 - 96%) than commercial control cigarettes
- Direction and relative magnitude of changes in corresponding biomarkers largely followed the changes in smoke chemistry

Smoke Constituent / (Biomarker)	TSS6 (vs CC6)		TSS1 (vs CC1)		BT1 (vs CC1)	
	Change in smoke yield (%)	Change in biomarker* (%)	Change in smoke yield (%)	Change in biomarker* (%)	Change in smoke yield (%)	Change in biomarker* (%)
Nicotine (TNeq)	-9	-11	-8	+34	+16	+23
NNK (NNAL)	-44	-11	-17	+31	-83	-46
NNN (NNN)	-50	-22	-69	-32	-96	-86
Acrolein (3-HPMA)	-55	-45	-60	-39	-43	-48
Crotonaldehyde (HMPMA)	-85	-75	-86	-58	-74	-63
1,3-butadiene (MHBMA)	-42	-63	-31	-46	+35	-54

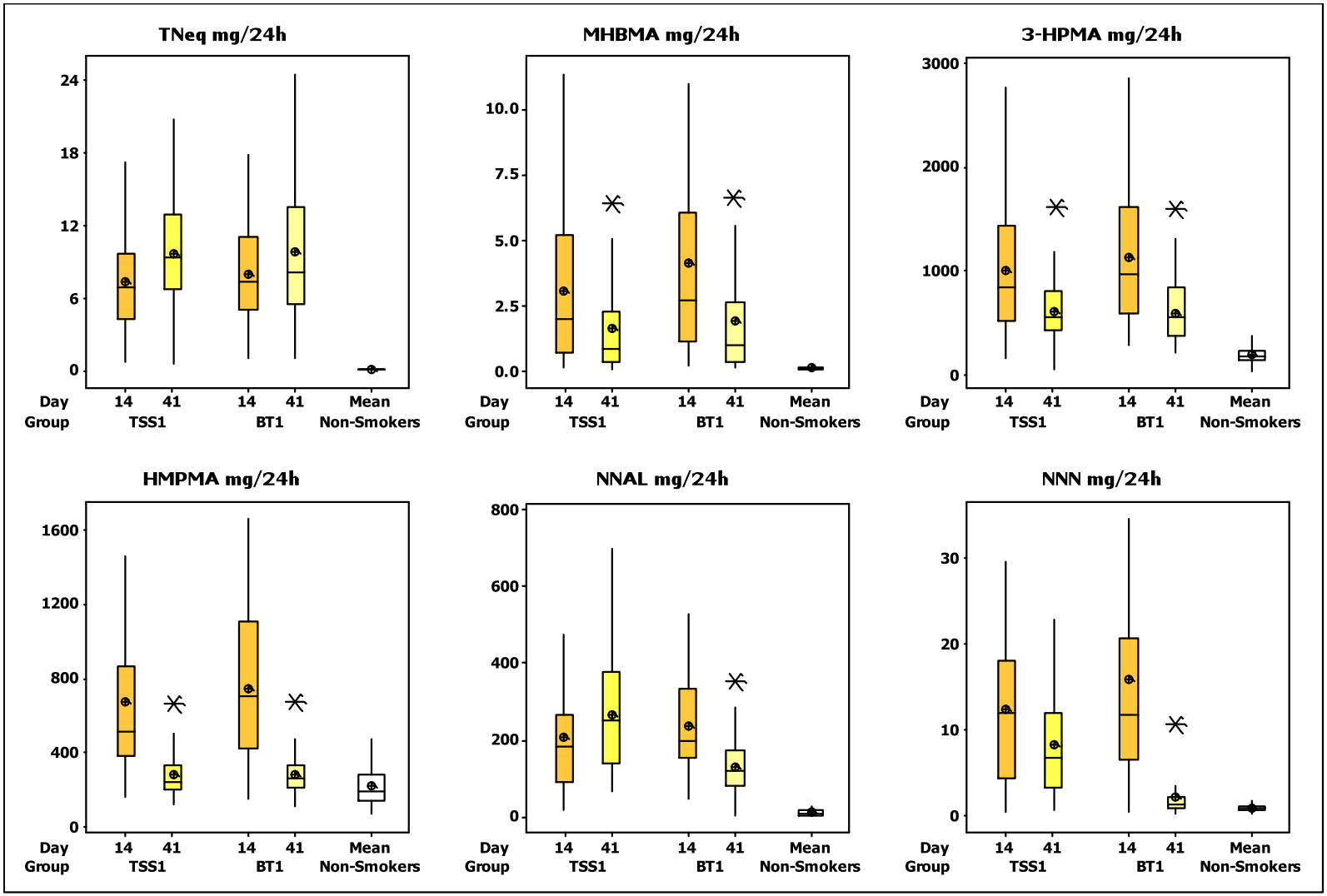
Key:
TNeq = Total Nicotine Equivalents
NNN = N-nitrosonornicotine
3-HPMA = 3-hydroxypropylmercapturic acid
MHBMA = monohydroxy-3-butenyl mercapturic acid
NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNAL= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
HMPMA = 3-hydroxy-1-methylpropylmercapturic acid
* Baseline (day 14) versus end of study (day 41)

Clinical Study 1 Example Results – 6mg products (TSS6 vs CC6)



- '*' denotes statistical significance ($p \leq 0.01$) using ANOVA followed by Tukey's HSD Test for multiple comparisons.
- Non-smoker biomarker levels shown for reference.

Clinical Study 1 Example Results – 1mg products (TSS1 vs CC1, BT1 vs CC1)



Conclusions from Clinical Study 1

- This study found that:
  - Smokers who switched to RTP cigarettes generally had reduced levels in the corresponding BoE (including BoEs for particulate and vapour phase related toxicants)
  - Different prototypes resulted in different levels of reduction in BoE, in some cases with reductions substantially greater than 50%
  - In all cases the average biomarker level was lower in the non-smoker group
- Further longer-term studies of RTPs are warranted in order to demonstrate continued exposure reduction.
- A manuscript has been prepared and is under consideration
- The next step is to begin to address the IOM second point; a reduction in risk - An RTP study evaluating Biomarkers of Biological Effect

Next Steps – Clinical Study 2

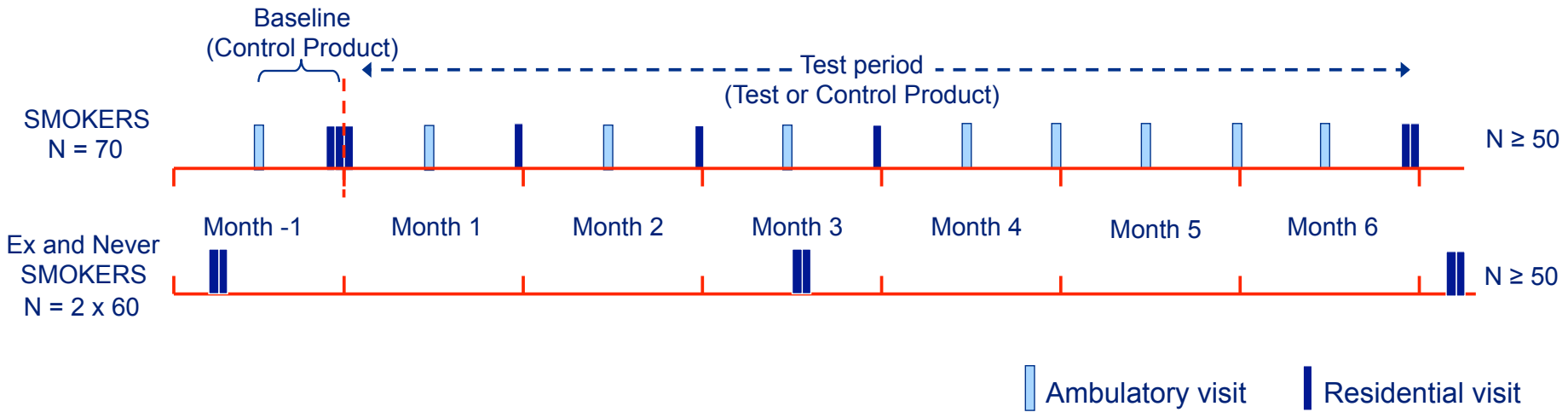
- To address point 2 of the IOM definition of a PREP:
  - a product that "(1) results in the substantial reduction in exposure to one or more tobacco toxicants and (2) can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects" (Stratton *et al*., 2001).

- To investigate the potential impact of changes in toxicant exposure on health risks, studies that also examine biomarkers of biological effect (BoBE) may be informative.
  - BoBE do not predict risk, but they are biological indicators of the body's response to cigarette smoke exposure, e.g. markers for inflammation and oxidative stress
  - Will necessitate an extended switching period to allow time for changes in these biomarkers to occur.

- Primary objectives will be to determine whether longer term use (6 months) of an RTP results in continued exposure reduction and a reduction in biomarkers of biological effect.

Clinical Study 2 Design

- Groups of smokers; 2 weeks baseline (commercial control) plus 6 months smoking commercial control or test (RTP) product
- Extended study, n=70 allows for attrition i.e. 50 to complete
- Two groups of non-smokers; ex-smokers and never smokers (n=2 x 60)



Clinical Study 2 Endpoints and Status

- Biomarkers of exposure
- Biomarkers of biological effect
- Biomarkers of effective dose (compliance)
- Mouth Level Exposure (filter analysis)
- Questionnaires; Sensory and Quality of Life
- Physiological measures
- Diary data
- Safety data

- To be conducted in Germany
- Ethical approval has been obtained
- Clinical conduct to commence in Q1 2012

Thank You

Any Questions?

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