Philip Morris International Research & Development

APPENDIX A6.1.4.2 C-REACTIVE PROTEIN (CRP)
HEALTH EFFECTS OF SMOKING CESSATION

Short Term Health Effects

C-reactive protein (CRP)

Dr. Gerhard Scherer

29th July 2015

Version: 1.0

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

TABLE OF CONTENTS

1 BACKGROUND 4
2 METHODS 5
3 FINDINGS 7
4 BIOMARKER-DISEASE LINK 9
4.1 Cardiovascular disease 9
4.2 Respiratory disease 10
5 SMOKING-BIOMARKER LINK 10
5.1 Smoking 11
5.2 Smoking cessation 21
5.3 Role in MRTP assessment 21
6 CONCLUSION 22
6.1 References used in the text 24
7 APPENDICES 37
7.1 Appendix 1 References of included studies (reference number in brackets) 38
7.2 Appendix 2 Inclusion criteria A 67
7.3 Appendix 3 Inclusion criteria B 74
7.4 Appendix 4 Inclusion criteria C 77
7.5 Appendix 5 Inclusion criteria D 80
7.6 Appendix 6 Inclusion criteria E 89
7.7 Appendix 7 Inclusion criteria F 92
7.8 Appendix 8 Inclusion criteria G 96
7.9 Appendix 9 Review articles 97
7.10 Appendix 10 Excluded articles 100

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

TABLE OF TABLES

Table 1. Number of articles according to source and inclusion criteria..... 8
Table 2. C-Reactive protein (CRP) levels in smokers, non-smokers and ex-smokers derived from various populations. 11
Table 3. Strength of evidence for the suitability of CRP as a biomarker of effect for MRTP assessment. 23

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

1 BACKGROUND

C-reactive protein (CRP) is an annular (ring-shaped), pentameric protein found in blood plasma and the levels of which rise in response to inflammation. CRP is a so-called acute-phase protein of hepatic origin that increases following interleukin-6 (IL6) secretion from macrophages, T cells and adipocytes. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells in order to activate the complement system via the C1Q [1].

CRP is a member of the pentraxin family of proteins and was the first Pattern Recognition Receptor (PRR) to be identified. It was named according its first identification as a protein in the serum of patients with acute inflammation that reacted with the C-polysaccharide of Pneumococcus [2].

CRP monomer consists of 224 amino acids with a molecular mass of 25106 Dalton. It aggregates to an annular pentamer with a discoid shape.

CRP levels in blood increase in response to a wide range of acute and chronic inflammatory conditions such as bacterial, viral, or fungal infections as well as rheumatic and other inflammatory diseases, malignancies and tissue injury and necrosis. These conditions cause the release of interleukin (IL)-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver. CRP plays a role in innate immunity as an early defense system against infections.

CRP rises up to a 50,000-fold within two hours of the onset of inflammation, and peaks at 48 hours. Its half-life of 18-19 hours is constant, and therefore its level is determined by the rate of production and hence the severity of the precipitating cause. CRP is thus a screen for inflammation [3].

Genetic factors are assumed to explain about 20-40 % of the CRP variation [4]. Heritability for elevated CRP levels is estimated to range from 39-52% [5]. Ancestry was found to play a significant role for blood CRP levels. In a meta-analysis of 89 studies, blacks in the USA had the highest (2.6 mg/L), South Asians the lowest (1.01 mg/L) mean CRP levels [6]. The distribution of CRP among Japanese was different from that among Westerners, however, the associations with cardiovascular disease (CVD) risk factors was similar [7].

Apart from being an important biomarker for inflammatory processes, CRP is also influenced by a number of other factors [8, 9]. In almost all epidemiological studies, an increase with age was reported [7, 10-12]. Epidemiological studies also revealed that women have higher CRP levels than men. Japanese males, however, were found to have higher serum CRP concentrations than Japanese females [7]. Physical activity lowers the CRP level in a dose-dependent manner [13]. The major life-style factors responsible for the CRP variation are diet, exercise and smoking [4]. High consumption of fruit and vegetables, carotinoids, vitamin C (but not vitamin E) and moderate alcohol intake are associated with lower CRP blood levels [14]. Fredrikson et al. [15] observed only a marginal association between CRP and individual dietary or lifestyle factors. It is not yet

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

clear whether caffeine or coffee consumption has an effect on CRP levels in the general population [16].

It has been suggested that the determination of blood CRP in the general population could act as an indicator of wellbeing [1]. Furthermore, it is assumed that factors related to an unhealthy life-style such as obesity, physical inactivity, smoking, and Western diet increase CRP levels in the general population. Asians have significantly lower (one tenth) serum CRP levels than Western populations, presumably because of the Asian diet [1].

In order to analyze CRP levels in the normal range (in contrast to the largely increased levels as a response to acute inflammations), high-sensitivity (hs) CRP assays have been developed, which are able to quantify CRP at levels as low as 0.04 mg/L (or even lower) and differentiate CRP values below 10 mg/L [14, 17]. CRP concentrations determined by these assays are often called 'hs-CRP'. In this document, only the term 'CRP' is used which includes the low-level CRP range.

Since the development of high-sensitivity CRP assays, this acute phase protein has been examined in a large number of studies. Increased CRP has been found to be associated with increasing age, body mass index (BMI), weight and reduced fitness levels. Significant differences in CRP levels relative to socioeconomic position, ethnicity and gender have also been reported [5].

The American Heart Association (AHA) and the U.S. Centers for Disease Control and Prevention (CDC) have defined risk groups as follows [4, 8, 18]:

- Low Risk: < 1.0 mg/L
- Average risk: 1.0 to 3.0 mg/L
- High risk: > 3.0 mg/L

It is recommended not to use CRP alone as a predictor for risk, but to combine it with elevated levels of cholesterol (C), low-density-lipoprotein (LDL)-C, triglycerides, and glucose.

2 METHODS

The published information for generating the present document was collected from the following sources:

(1) Monographs on biomarkers of effect and smoking:

- US Surgeon General Report 2010 [19]
- Life Sciences Research Office (LSRO) Report of 2007 [20]

(2) References related to CRP extracted from the two monographs (Source 1)

(3) Search 1 in the PubMed literature data base on 23.06.2015 for reviews on CRP; search string: "(c-reactive protein[Title] OR CRP[Title]) AND smok* Filters: Review; published in the last 10 years; Humans"

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(4) Search 2 in the PubMed literature data base on 23.06.2015 for references on CRP and smoking or nicotine; search string: "((((c-reactive protein[Title] OR CRP[Title])))) AND (smoking[Title] OR smokers[Title] OR tobacco[Title] OR nicotine[Title] OR cigarettes[Title]) Filters: published in the last 10 years)"

(5) Search 3 in the PubMed literature data base on 23.06.2015 for references on CRP and CVD; search string: "(((((((c-reactive protein[Title] OR CRP[Title])))) AND cardiovascular disease[Title]) AND free full text[sb] AND "last 5 years"[PDat] AND Humans[Mesh])) AND English[Language] Filters: published in the last 5 years; Humans"

(6) Search 4 in the PubMed literature data base on 23.06.2015 for references on CRP and respiratory disease; search string: "((((c-reactive protein[Title] OR CRP[Title])))) AND respiratory[Title] Filters: published in the last 5 years; Humans"

(7) Search 5 in the PubMed literature data base on 23.06.2015 for references on CRP and cancer (limited to smoking-related cancers); search string: (((((((c-reactive protein[Title] OR CRP[Title])))) AND cancer[Title]))) AND (lung[Title/Abstract] OR kidney[Title/Abstract] OR pancreas[Title/Abstract] OR bladder[Title/Abstract]) Filters: published in the last 5 years; Humans"

(8) Cited articles from Sources 2 – 7 with relevance for the topics of interest.

Studies were selected for evaluations in the chapters 'Biomarker-disease link' and 'Smoking-biomarker link' according to the following inclusion criteria:

A: Association between CRP and (CVD) in a human cohort was investigated

B: Association between CRP and respiratory diseases in a human cohort was investigated

C: Association between CRP and any other (smoking-related) disease in a human cohort was investigated

D: Differences in CRP levels between smokers and non-smokers were investigated and suitable data presented

E: The dose-response relationship between smoking intensity (determined for example by daily cigarette consumption, pack-years or cotinine) and CRP level was studied and suitable data presented

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

F: The effect of smoking cessation on the CRP level was studied and suitable data presented

G: The effect of switching from conventional cigarettes to modified risk tobacco products (MRTPs) or nicotine products on the CRP level was investigated

R: Review article on CRP

Reviews were used for generating the chapter "Background" and, if suitable, also for chapters on the CRP link to diseases and smoking.

1. Studies retrieved, but not fulfilling any of the inclusion criteria A – G and R were excluded from the evaluation (assigned as '01 to 05' in Appendix 1 together with the reason for exclusion).

3 FINDINGS

From Source 1 (Monographs) [19, 20], 22 articles [3, 8, 9, 18, 21-38] were extracted (9 originating from the Surgeon General Report 2010, 15 from LSRO Report, 2 overlaps occurred).

The distribution of articles according to the Sources 1 – 8 described in chapter 'Methods' and according the inclusion criteria A – G and R are summarized in Table 1. The individual articles according to sources and assignment to inclusion and exclusion criteria are compiled in Appendix 1.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 1. Number of articles according to source and inclusion criteria.

Source (Description)	All	Relevant	Inclusion criteria[a]								Ex-cluded
			A	B	C	D	E	F	G	R	
1 (Monographs)	2	2	2	0	0	2	1	2	0	2	0
2 (Articles extr. from 1)	22	17	12	0	0	6	4	3	1	0	5
3 (Search 1, reviews)	14	14	10	0	2	1	1	1	0	12	0
4 (Search 2, smoking)	43	27	1	3	2	26	11	8	0	0	16
5 (Search 3, CVD)	25	13	13	0	0	1	0	0	0	1	12
6 (Search 4, resp. dis.)	17	8	0	8	0	0	0	0	0	0	9
7 (Search 5, cancer other diseases)	26	14	0	1	14	0	0	0	0	1	12
8 (Cited articles in 2 - 7)	22	22	8	0	1	20	6	10	1	0	0
Sum	171[b]	116	46	12	19	56	23	24	2	16	54

[a] Note that an article could fulfil several inclusion criteria

[b] Deviation from the 169 articles listed in Appendix 1 is caused by some overlap between the search results yielding identical articles

Of the 171 articles retrieved from the various sources, 116 show relevance to be considered for the generation of this document, 54 publications were of no or very limited relevance for this purpose and were, therefore, excluded. Five reasons for exclusion are given in Appendix 1.

Most articles retrieved deal with the criteria CVD (A), other diseases (C) and smoking (D – G) or were reviews (R). No separate search for the association of CRP with other diseases was performed, since the category ‘other diseases’ was already represented in the other searches (particularly in Source 3). CRP is also important in respiratory diseases (B), particularly infections, as is reflected by the fact that 12 articles were retrieved for this topic. There were 105 articles which considered the relationship between CRP and smoking (D – G). The aspect of smoking cessation (F) was dealt with in 24 studies which provided CRP data for ex-smokers. The dose-relationship between smoking and CRP levels (E) was investigated in 23 articles. Two articles were found, which deal with the

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

changes in CRP levels after switching to MRTPs or nicotine products (G), however, in only one article CRP data for evaluation were provided.

It should be noted that the classification of the retrieved articles was done after a first inspection (usually by reading the abstract). The final classification can somewhat deviate from this assignment. However, the distribution of the articles according the defined criteria was very similar to that shown in Table 1, thus, these numbers reflect rather well the knowledge and the load of evidence available for the various categories.

4 BIOMARKER-DISEASE LINK

4.1 Cardiovascular disease

The association of CRP with CVD and coronary heart disease (CHD) has been investigated in a large number of both prospective and retrospective (case-control) epidemiological studies [11, 18, 27, 39-42]. As a general observation, it was found that CRP is moderately but significantly associated with these diseases. Despite the fact that some uncertainties and controversies remain [39, 40]. CRP can be regarded as an independent predictor for CVD and CHD, in particular for atherosclerosis. CR

P has, therefore, increasingly been used as a risk factor for CVD in addition to the 'traditional' risk factors (age, hypertension, cholesterol, family history and cigarette smoking) [10, 32]. It is most probable that CRP indicates a low-grade inflammation, which is known to play a role in the pathogenesis of atherosclerosis, rather than CRP taking part in the pathogenesis of the diseases [8, 11].

In addition to being an indicator of low-grade vascular inflammation (an important risk factor for CVD,) CRP has also been thought to have a function as a direct partaker in lesion formation through proatherosclerotic and proinflammatory mechanisms [37]. Thus CRP may not just be a marker of atherosclerosis and coronary events, but also a mediator of this disease because it contributes to the substrate underlying lesion formation, plaque rupture, and coronary thrombosis. There is experimental evidence that CRP may contribute to the formation of foam cells in atherosclerotic lesions by causing aggregation of LDL particles [28, 32]. It has also been suggested that CRP may directly affect expression of adhesion molecules, impact fibrinolysis and inhibit the production of nitric oxide and prostacyclin (prostaglandin I2, PGI2) [18, 43]. Furthermore, CRP may play a causal role in apoptosis by regulating the gene GADD153 [24].

The direct involvement in the pathogenesis of atherosclerosis would make CRP a suitable target for prevention and treatment of this disease. However, there is presently scientific consensus that the primary aim for preventing CVD is to modify the traditional risk factors such as hypertension, unhealthy diet, obesity, physical inactivity and cigarette smoking [34].

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

4.2 Respiratory disease

CRP is an established clinical marker for respiratory tract infections [44-49]. CRP also proved to be a suitable biomarker for diagnosis, prognosis and treatment monitoring of COPD patients [50-53]. Forced expiratory volume in 1 second (FEV1) was found to be inversely correlated with blood CRP levels (r=-0.317, P= 0.002) [50]. This finding was independent of the ever-smoking status. Furthermore, it was reported that a 10% increase in CRP was associated with a lowering of the FEV1 value by 3.0 – 4.7 mL [54].

There is scientific accordance that CRP is not causally related to any type of cancer. Rather, it is associated with the risk of all-cancer mortality and is of diagnostic and prognostic value for various types of cancer [55-58].

CRP was found to have excellent predictive power for bronchial dysplasia, which is a precursor lesion to lung cancer [59]. Since inflammation in the lung plays an import role in lung cancer development and prognosis [53], it is not unexpected that significant associations between CRP and this type of cancer were frequently reported [57, 58, 60-65].

CRP was also found to have good prognostic properties for gastric cancer [66]. Furthermore, CRP was reported to be possibly associated with breast, prostate and colorectal cancer [57]. No associations were found for pancreas [67] and head and neck cancer [68].

5 SMOKING-BIOMARKER LINK

As is evident from the following sections, a large number of studies have been published on the association between smoking and blood CRP levels. In most of them, a direct relationship between the two factors has been observed. This raises the question of the mechanism of this relationship.

The most obvious mechanism for the association between CRP and smoking is that smoking induces chronic inflammation not only in the airways, but also in the blood vessels which may lead to increased systemic CRP levels [69, 70]. It has also been suggested that smoking may lower insulin resistance which has been found to increase CRP levels [69]. Additionally, smoking might influence adipose tissue and cause the release of IL-6 resulting in elevated hepatic CRP synthesis [71]. Furthermore, in vitro experiments have shown that nicotine can upregulate CRP synthesis in macrophages [72, 73]. Finally, it has been speculated that the dietary intake of n-3 polyunsaturated fatty acids (n-3 PUFA, which may attenuate inflammatory reactions), which were found to be lower in smokers, is responsible for the elevated CRP levels observed in smokers [74].

Of the discussed possible mechanisms, the smoking-related induction of chronic inflammation is the most plausible and probable one. The observed delayed reduction in CRP levels in former smokers (requiring several years) before reaching the levels observed in never smokers strongly supports this mechanism.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

5.1 Smoking

Due to the large number of data available, Table 2 contains only a selection of published studies.

Table 2 has been compiled from data obtained from 21 of these studies. Of these, 6 reported separate CRP data for both sexes leading to 27 possible comparisons of smokers and non-smokers. Twenty (74%) of the differences between smokers and non-smokers were statistically significant (at least in the highest cigarette consumption group). Most of the non-significant differences between smokers and nonsmokers were reported for women.

Tonstad et al. [5] published a similar table including 6 studies, of which 3 studies [12, 33, 75] were also included in Table 2, Table 3 other studies [38, 76, 77] were not. Four of 5 (80%) comparisons between smokers and nonsmokers were found to be statistically significant. The percentage of significant findings, therefore, is very similar in both groups of studies.

Table 2. C-Reactive protein (CRP) levels in smokers, non-smokers and ex-smokers derived from various populations.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Bermudez et al. [12]	Healthy women enrolled in the Women's Health Study (USA), mean age 60 years	Serum CRP were determined with an BN II analyzer (Dade Behring), mg/dL, mean±SD[a]: Current S (N=9): 0.3±3.1	Serum CRP were determined with an BN II analyzer (Dade Behring), mg/dL, mean±SD: Former S (N=96): 0.3±3.0 Never S (N=150): 0.2±3.0	Differences between groups: P=0.04

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Fröhlich et al. [75]	Men and women from the MONICA Study Augsburg (Germany), aged 25-74 years	Plasma CRP was determined with a immunoradiometric assay, mg/L, means: Men Occasional S (N=74): 1.4 Regular S (N=609): 1.9 Women Occasional S (N=58): 1.2 Regular S (N=408): 1.5	Plasma CRP was determined with a immunoradiometric assay, mg/L, means: Men Never S (N=748): 1.0 Ex-S (N=874): 1.3 Women Never S (N=1315): 1.4 Ex-S (N=430): 1.4	Differences between groups: Men: p<0.001 Women: Not significant
Bazzano et al. [78]	Participants in the Third National Health and Nutrition Exami-nation Survey (NHANES) in the USA (40+ years old)	Serum CRP was determined with a latex-enhanced nephelometric method, results were expressed as adjusted odd ratios of clinically ele-vated CRP levels (95%-CI[b]): S, 1-9 cig/d (N=?, all S: 4945): 1.3 (0.9-2.1) S, 10-19 cig/d: 1.3 (0.9-1.9) S, 20+ cig/d: 2.1 (1.6-2.8)	Serum CRP was determined with a latex-enhanced nephelometric method, results were expressed as adjusted odd ratios of clinically elevated CRP levels (95%-CI): Never S (N=9864) 1.0	P for trend: 0.001 There was also a significant dose-response relationship between CRP and pack-year as well as CRP and serum cotinine

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Panagiotakos et al. [79]	Subjects from the ATTICA Study in Greece, no evidence for present of past CVD, mean age about 45-50 years	Serum CRP was determined with a BN II analyzer (Dade Behring), mg/dL, mean±SD: Men Current S (N=544): 1.9±1.2 Women Current S (N=441): 1.7±1.3	Serum CRP was determined with a BN II analyzer (Dade Behring), mg/dL, mean±SD: Men Former S (N=227): 1.4±1.3 Never S (N=357): 1.4±1.1 Women Former S (N=75): 1.4±1.1 Never S (N=638): 1.5±1.1	Current vs never S: Men: P<0.001 Women: P<0.05 Former vs current S: Men: P<0.01 Women: P<0.05 Former vs never S: Men and women: Not significant
Ohsawa et al. [33]	Healthy Japanese men, 40-69 years old, CRP>10mg/l excluded (acute inflammation)	Serum CRP analyzed with a latex-enhanced immoturbimetric method, mg/L, geometric mean (95%-CI) Current S (N=762): 0.6 (0.5-0.6)	Serum CRP analyzed with a latex-enhanced immoturbimetric method, mg/L, geometric mean (95%-CI) NS (N=661): 0.4 (0.4-0.5) Past S (N=503): 0.5 (0.4-0.5)	Difference between any group: P<0.05

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Garcia-Lorda et al. [80]	Men and women from a Spanish Mediterranean community, aged 18-74 years	Serum CRP measured by immunoturbimetry, mg/L, geometric mean±SD: Men: Occasional S (N=17): 1.1±2.8 Regular S (N=179):1.6±2.9 Women: Occasional S (N=26): 1.6±3.1 Regular S (N=168):1.4±2.8	Serum CRP measured by immunoturbimetry, mg/L, geometric mean±SD: Men: Never S (N=296):1.4±2.7 Women: Never S (N=443):1.5±2.8 Regular S (N=168):1.4±2.8	Differences between groups: Men: p=0.161 Women: P=0.819
Madsen et al. [70]	Men from the Oslo population, 67-77 years old (Oslo II Health Study), CRP>10mg/l excluded (acute inflammation)	CRP in serum was analyzed with a latex-enhanced assay, mg/L, geometric mean±SD: Current S (N=618): 2.1±2.4	CRP in serum was analyzed with a latex-enhanced assay, mg/L, geometric mean (SD): NS (N=1096): 1.3±2.5 Former S (N=2030): 1.6±2.5	ANOVA: P<0.001

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Dietrich et al. [81]	Subjects from the NHANES Study (1999-2002) in the US, age: 20+ years	CRP in serum was analyzed with latex-enhanced nephelometry, mg/L, mean±SD: Males: Current S: 4.5±7.2 Females: Current S: 5.9±11.0	CRP in serum analyzed with latex-enhanced nephelometry, mg/L, mean±SD: Males: Never S: 3.4±8.5 Former S: 4.0±9.0 Females: Never S: 5.5±7.6 Former S: 5.7±7.5	No significances given for differences between groups. CRP significantly increases with CPD in men of all age groups, but not in women. Exogenous hormones modified the effect of smoking on CRP.
Saijo et al. [82]	Employees from a company in Japan, investigated during a health check-up, only men, aged 35-60 years	Serum CRP was analyzed with a latex-enhanced nephlometric immunoassay, mg/L, median (IQR[c]): Current S (N=165): 0.051 (0.026-0.092)	Serum CRP analyzed with a latex-enhanced nephlometric immunoassay, mg/L, median (IQR): NS (N=182): 0.036 (0.020-0.071)	S vs NS: P<0.013

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Levitzky et al. [83]	Subjects from the Framingham Offspring cohort, mean age ~ 60 years	Serum CRP was determined with a BN 100 nephelometer (Dade Behring), mg/L, geometric mean (95%-CI): S, acute: ≤6h (N=237): 3.2 (2.8-3.6) S, > 6h ago (N=134): 2.6 (2.2-3.1)	Serum CRP was determined with a BN 100 nephelometer (Dade Behring), mg/L, geometric mean (95%-CI): Never S (N=1149): 2.0 (1.9-2.1) Former S (N=1424): 2.3 (2.1-2.4)	Differences to never S, for all groups: P<0.0045
Hastie et al. [84]	Healthy subjects from the Scottish Heart Study, aged 16+ years, subjects	CRP in serum was analyzed with latex-enhanced nephelometry, mg/L, median (IQR): Current S (N=1345): 1.9 (0.7-4.0)	CRP in serum was analyzed with latex-enhanced nephelometry, mg/L, median (IQR): Ex-S (N=892): 1.6 (0.7-3.7) Never S (N=1790): 1.1 (0.5-2.7)	Differences between groups (Kruskal-Wallis-test): P<0.001 Ex-S having stopped ≥20 years ago: Not significantly different from NS. CRP increased with pack-years in current and Ex-S

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
O'Loughlin et al. [85]	Canadian adolescents of the ages 13 and 16 years, subjects with health conditions affecting CRP were excluded.	Plasma CRP was measured with a immunochemical assay, data presented as adjusted odd ratio with 95%-CI range: S (smoked in past month): Light, 1cig/2d (N=162): 1.4 (0.7-2.8) Moderate, 4 cig/d (N=114): 2.1 (1.0-4.4) Heavy, 8 cig/d (N=137): 2.4 (1.2-4.9)	Plasma CRP was measured with a immunochemical assay, data presented as adjusted odd ratio with 95%-CI range: Never smoked (N=548): 1.0	S vs never S: Only heavy S significantly different from NS (P=0.0130)
Ahonen et al. [71]	Middle-aged (45-47 years) men and women from the Finish population, diabetics and subjects with hs-CRP>10pg/ml excluded	CRP analyzed with an hs-CRP assay, pg/mL, mean±SD: Men S (N=125): 1.6 ±1.7 Women: S (N=104): 1.3 (from graph)	CRP analyzed with an hs-CRP assay, pg/mL, mean±SD: Men NS (N=125): 1.2±1.4 Women: S (N=104): 1.5 (from graph)	S vs NS: Men: P<0.018 Women: Not significant

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Calapai et al. [86]	Healthy males and females selected for a clinical study in Italy (age- and gender-matched for the 3 groups), mean age ~ 30 years	Serum CRP was determined by an immunoturbimetric assay, mg/dL, geometric mean (95%-CI): Moderate S, average 10.8cig/d (N=20): 0.1 (0.07-0.2) Heavy S, average 20.2cig/d (N=20): 0.1 (0.1-0.2)	Serum CRP was determined by an immunoturbimetric assay, mg/dL, geometric mean (95%-CI): Never S, (N=20): 0.08 (0.06-0.12)	S vs NS: Not significant
Hanyu et al. [69]	Healthy men (diabetics and subjects with inflammations were excluded) aged 20-68 years from Japan	CRP in plasma was analyzed with nephelometry, mg/L, mean±SD: S (N=67): 0.7±0.5	CRP in plasma was analyzed with nephelometry, mg/L, mean±SD: NS (N=54): 0.4±0.5	S vs NS: P<0.0001
Azar and Richard [87]	Healthy students (males and females) from Canada (mean age 18.9 years)	CRP in saliva analyzed with an ELISA method, ng/mL, mean±SD: S (N=10): 2780.1±2501.8	CRP in saliva analyzed with an ELISA method, ng/mL, mean±SD: NS (N=13): 371.6±255.2 Passive S (N=22): 1826.5±2744.3	S vs NS: P<0.001 Passive vs NS: P=0.011 Passive S vs S: Not significant

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Frost-Pineda et al. [88]	Healthy subjects (males and females, age 21+ years) from the US (Total Exposure Study); subjects with CRP>10mg/l were excluded	Serum CRP was determined by immunonephelometry, mean±SD, mg/L: S (N=3266): 2.8±2.6	Serum CRP was determined by immunonephelometry, mean±SD, mg/L: NS (N=1002): 2.4±2.5	S vs NS: P<0.05
Le-Ha et al. [89]	Australian adolescents, 17 years old, girls: using/non using oral contracep-tives, OC)	CRP in serum, mg/L, mean (95%-CI): Boys, S (N=82): 0.6 (0.5, 0.8) Girls not using OC, S (N=61): 1.0 (1.0, 1.3) Girls using OC, S (N=37) 1.3 (0.9, 2.1)	CRP in serum, mg/L, mean (95%-CI): Boys, NS (N=464): 0.5 (0.4, 0.5) Girls not using OC, NS (N=284): 0.5 (0.5, 0.6) Girls using OC, NS (N=122): 1.5 (1.2, 1.8)	S vs NS: P<0.001 (in all corresponding groups, except for girls taking OC)
Khand et al. [90]	Healthy men from two villages in Pakistan, 20-40 years old	CRP in serum was analyzed with a 'standard kit', mg/L, mean±SD: S (N=48): 14.6±0.2	CRP in serum analyzed with a 'standard kit', mg/L, mean±SD: NS (N=48): 4.8±0.2	S vs NS: P<0.001
Kleber et al. [72]	Patients with acute coronary syndromes, but clinically stable, the Ludwigshafen Risk and Cardiovascular Health Study	hs-CRP in plasma was analyzed with a immunonephelometric method, ng/mL, median (IQR): S (N=777): 4.9 (1.8-10.3)	hs-CRP in plasma was analyzed with a immunonephelometric method, ng/mL, median (IQR): NS (N=1178): 2.7 (1.2-7.9)	S vs NS: P<0.001

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Author, (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Kawada et al. [91]	Japanese workers (males), 30-60 years old	CRP in serum, analyzed with a latex-turbidity assays, mg/L, mean±SD: Current S, <20cig/d (N=1492): 0.4±1.0 Current S, ≥20 cig/d N=(1266): 0.4±1.0	CRP in serum, analyzed with a latex-turbidity assays, mg/L, mean±SD: Former S, <1 y (N=61): 0.5±1.2 Former S,1-6 y (N=695): 0.3±1.0 Former S, >6 y (N=205): 0.3±1.1 Never S (N=1512): 0.4±1.0	Various S groups vs NS: Only S, ≥20 cig/d significant (p<0.05)

[a] SD: Standard deviation; [b] CI: Confidence interval; [c] IQR: Inter-quartile range

Levitzky et al. [83], noted that significantly higher CRP levels were observed after acute smoking (exposure ≤ 6h ago) compared to smoking > 6h ago (Table 2). This is somewhat at odds with the time pattern of the CRP levels after quitting smoking (see section 'Smoking cessation') and certainly requires further investigation.

Furthermore, in three studies [79, 87, 92] significant increases of CRP in passive smokers compared to unexposed nonsmokers were reported, whereas in two other investigations [70, 93], no significant effect of exposure to environmental tobacco smoke (ETS) was found.

The dose-response relationship between blood CRP levels and smoking has been investigated in a relatively large number of studies.The smoking-dose was either assessed by cigarettes consumed per day (CPD) [22, 31, 33, 70, 75, 77, 78, 81, 82, 85, 91, 94-97], pack-years [33, 35, 70, 75, 78, 84], duration of smoking [75, 94], cotinine in body fluids [87, 96] or carbon monoxide in exhaled breath [96].

The findings can be summarized by the statement that almost all studies showed a trend for increasing CRP levels with increasing smoking dose or years of smoking. However, in only about one half of the studies did the dose-response relationship reach statistical significance.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

5.2 Smoking cessation

The effect of smoking cessation on blood CRP levels in smokers has been investigated in an appreciable number of studies. Ten of the 27 data sets summarized in Table 2 provided CRP data for former smokers. In six of these data sets [12, 33, 70, 75, 79, 83], CRP levels of ex-smokers were in between those of never and current smokers. In four data sets [75, 79, 84, 91], CRP levels after long-term smoking cession were not significantly different from never smokers. Similar results were also reported by other authors [33, 78, 97, 98].

In some studies [22, 33, 38, 76, 77, 81, 84, 91, 92, 96], the time-dependence of CRP levels after smoking cessation was investigated. The data reported allow the general conclusion that about 5 years of smoking cessation are required before the never smoker levels for CRP are reached.

This conclusion is in accordance with that of Tonstad and Cowan [5] who stated that the CRP levels in former smokers fail to fall immediately upon cessation, which reflects the fact that the underlying tissue damage caused by smoking takes some time to recover.

5.3 Role in MRTP assessment

In a long-term switching study [99], CRP was determined at baseline (when subjects were still smoking conventional cigarettes) and 12 months after switching to an electrically heated cigarette smoking system (EHCSS). CRP concentrations in the smokers who continued smoking conventional cigarettes were 2.3±0.4 (standard error of the mean) mg/L at baseline and 2.3±0.1 mg/L 12 months later. Corresponding values for the switchers were 2.2±0.3 and 1.8±0.1 mg/L. The reduction in the CRP levels after switching to EHCSS was not statistically significant. This result, however, would be in accordance with smoking cessation studies summarized in the previous section, which show longer time periods to achieve non-smoking levels for CRP.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

6 CONCLUSION

CRP is a well-established biomarker of inflammation, suitable for both clinical purposes and epidemiological studies. The association between CRP and the risk for CVD has been documented in many large, prospective epidemiological studies. Furthermore, CRP was also reported to be predictive for respiratory diseases and various types of cancer, in particular lung cancer.

At present, there is consensus that CRP is an indicator for acute and chronic inflammation processes rather than being directly involved in the pathophysiological processes of CVD, COPD or cancer.

There is strong evidence that smoking is associated with an increase of blood CRP levels. This association was found to be smoking dose-dependent in many investigations. The dose-response relationship was reported to be statistically significant in about half of the studies. Long-term smoking cessation leads to a reduction in CRP levels of former smokers although it requires, on average, about 5 years of smoking cessation before non-smoker CRP levels are achieved. The effects of acute smoking and quitting on blood CRP levels have not yet been systematically investigated.

Only one long-term (12 months) switching study has been published [99]. In this study smokers of conventional cigarettes switched to an EHCSS. A (not statistically significant) reduction in CRP levels was observed one year after switching. Given the smoking cessation results, the switching period of one year might be too short to achieve significant reductions in the CRP level.

The most probable mechanism for the observed relationship between CRP and smoking is that smoking induces chronic inflammation in the airways and blood vessels. The evidence for other possible mechanisms is as yet rather sparse.

A major limitation of the suitability of CRP as biomarker of effect for the evaluation of MRTPs is the rather long time period required (~ 5 years) to achieve non-smoker levels after switching. However, CRP might qualify for long-term investigations of the biological effect of MRTPs (e.g. post-market studies).

The evidence for suitability of CRP as a biomarker of effect in the assessment of MRTPs is summarized in Table 3.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 3. Strength of evidence for the suitability of CRP as a biomarker of effect for MRTP assessment.

Property	Evidence
Biological plausibility	Due to its biological properties (indicator of acute and chronic inflammatory processes), CRP can be regarded as a suitable biomarker of risk for the development of smoking-related diseases such as CVD, COPD and lung cancer. Elevated CRP is an indicator of a pathological process (inflammation), rather than a causal involvement in the pathogenesis. Since smoking can induce inflammation in the airways and the blood vessels, the observed association between CRP and smoking is biologically plausible.
Dose-response	Differences between smokers and non-smokers (zero dose) were reported for various groups of subjects including healthy people (see Table 2). There is consistent evidence that blood CRP levels tend to increase with the smoking dose.
Benchmark to cessation	There is consistent evidence that smoking cessation leads to a reduction in CRP to levels between current and never smokers (Table 2, Section "Smoking cessation"). To achieve non-smoker CRP levels, about 5 years of smoking cessation are required. No investigations of the acute effects of smoking cessation on the CRP concentrations are available.
Consistency[a]	Available data for CRP and smoking are consistent in terms of differences between smokers and non-smokers, dose-response and smoking cessation.
Coherence[b]	In this document, almost exclusively human data from clinical and epidemiological studies were evaluated. Also not in the focus of this review, no evidence was found that results from animal and *in vitro* studies would deviate from the human data.

[a] Consistent findings in various studies strengthens the likelihood that the finding is true

[b] Coherence of findings from epidemiological, laboratory, animal and *in vitro* studies increases the likelihood that the result is true

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

6.1 References used in the text

1. Kao PC, Shiesh SC, Wu TJ. Serum C-reactive protein as a marker for wellness assessment. Ann Clin Lab Sci. [Review]. 2006 Spring;36(2):163-9.

2. Tillett WS, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. The Journal of experimental medicine1930;52(4):561-71.

3. Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clin Invest. [Research Support, Non-U.S. Gov't]. 1993 Apr;91(4):1351-7.

4. Ridker PM, Silvertown JD. Inflammation, C-reactive protein, and atherothrombosis. J Periodontol. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2008 Aug;79(8 Suppl):1544-51. doi: 10.902/jop.2008.080249.

5. Tonstad S, Cowan JL. C-reactive protein as a predictor of disease in smokers and former smokers: a review. Int J Clin Pract. [Review]. 2009 Nov;63(11):1634-41. doi: 10.111/j.742-241.2009.02179.x. Epub 2009 Aug 29.

6. Shah T, Newcombe P, Smeeth L, Addo J, Casas JP, Whittaker J, Miller MA, Tinworth L, Jeffery S, Strazzullo P, Cappuccio FP, Hingorani AD. Ancestry as a determinant of mean population C-reactive protein values: implications for cardiovascular risk prediction. Circ Cardiovasc Genet. [Meta-Analysis

   Research Support, Non-U.S. Gov't Review]. 2010 Oct;3(5):436-44. doi: 10.1161/CIRCGENETICS.110.957431. Epub 2010 Sep 28.

7. Yamada S, Gotoh T, Nakashima Y, Kayaba K, Ishikawa S, Nago N, Nakamura Y, Itoh Y, Kajii E. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population : Jichi Medical School Cohort Study. Am J Epidemiol. [Research Support, Non-U.S. Gov't]. 2001 Jun 15;153(12):1183-90.

8. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, Jr., Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. [Guideline Practice Guideline Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2003 Jan 28;107(3):499-511.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

9. Rackley CE. New clinical markers predictive of cardiovascular disease: the role of inflammatory mediators. Cardiol Rev. [Review]. 2004 May-Jun;12(3):151-7.

10. Rudolf J, Lewandrowski KB. Cholesterol, lipoproteins, high-sensitivity c-reactive protein, and other risk factors for atherosclerosis. Clin Lab Med. [Review]. 2014 Mar

doi: 10;2014 Mar;34(1):113-27.

11. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL, Pepys MB. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 1999 Jan 19;99(2):237-42.

12. Bermudez EA, Rifai N, Buring J, Manson JE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler Thromb Vasc Biol. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2002 Oct 1;22(10):1668-73.

13. Plaisance EP, Grandjean PW. Physical activity and high-sensitivity C-reactive protein. Sports Med. [Review]. 2006;36(5):443-58.

14. Nanri A, Moore MA, Kono S. Impact of C-reactive protein on disease risk and its relation to dietary factors. Asian Pac J Cancer Prev. [Research Support, Non-U.S. Gov't Review]. 2007 Apr-Jun;8(2):167-77.

15. Fredrikson GN, Hedblad B, Nilsson JA, Alm R, Berglund G, Nilsson J. Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma C-reactive protein levels. Metabolism. [Research Support, Non-U.S. Gov't]. 2004 Nov;53(11):1436-42.

16. Rodrigues IM, Klein LC. Boiled or filtered coffee? Effects of coffee and caffeine on cholesterol, fibrinogen and C-reactive protein. Toxicol Rev. [Research Support, U.S. Gov't, Non-P.H.S. Review]. 2006;25(1):55-69.

17. Corrado E, Novo S. [High sensitivity of C-reactive protein in primary prevention]. G Ital Cardiol (Rome). [Review]. 2007 Jun;8(6):327-34.

18. Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation. [Review]. 2004 Jun 29;109(25 Suppl 1):IV6-19.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

19. US Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease A Report of the Surgeon General2010.

20. Life Sciences Research Office (LSRO). Biological effects assessment in the evaluation of potential reduced-risk tobacco products. Brownawell AM, editor. Bethesda, Maryland, USA2007.

21. Axelsson T, Jansson PA, Smith U, Eliasson B. Nicotine infusion acutely impairs insulin sensitivity in type 2 diabetic patients but not in healthy subjects. J Intern Med. [Clinical Trial Randomized Controlled Trial]. 2001 Jun;249(6):539-44.

22. Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. PLoS Med2005 Jun;2(6):e160. Epub 2005 Jun 28.

23. Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. Journal of the American College of Cardiology1993 Oct;22(4):1159-67.

24. Blaschke F, Bruemmer D, Yin F, Takata Y, Wang W, Fishbein MC, Okura T, Higaki J, Graf K, Fleck E, Hsueh WA, Law RE. C-reactive protein induces apoptosis in human coronary vascular smooth muscle cells. Circulation. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2004 Aug 3;110(5):579-87. Epub 2004 Jul 26.

25. Burke AP, Tracy RP, Kolodgie F, Malcom GT, Zieske A, Kutys R, Pestaner J, Smialek J, Virmani R. Elevated C-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies. Circulation. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. 2002 Apr 30;105(17):2019-23.

26. Chakraborti T, Mandal A, Mandal M, Das S, Chakraborti S. Complement activation in heart diseases. Role of oxidants. Cell Signal. [Research Support, Non-U.S. Gov't Review]. 2000 Oct;12(9-10):607-17.

27. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. [Research Support, Non-U.S. Gov't]. 2004 Apr 1;350(14):1387-97.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

28. Fu T, Borensztajn J. Macrophage uptake of low-density lipoprotein bound to aggregated C-reactive protein: possible mechanism of foam-cell formation in atherosclerotic lesions. Biochem J. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. 2002 Aug 15;366(Pt 1):195-201.

29. Jensen EJ, Pedersen B, Frederiksen R, Dahl R. Prospective study on the effect of smoking and nicotine substitution on leucocyte blood counts and relation between blood leucocytes and lung function. Thorax1998 Sep;53(9):784-9.

30. Joseph AM, Hecht SS, Murphy SE, Carmella SG, Le CT, Zhang Y, Han S, Hatsukami DK. Relationships between cigarette consumption and biomarkers of tobacco toxin exposure. Cancer Epidemiol Biomarkers Prev. [Research Support, N.I.H., Extramural]. 2005 Dec;14(12):2963-8.

31. Joseph AM, Hecht SS, Murphy SE, Lando H, Carmella SG, Gross M, Bliss R, Le CT, Hatsukami DK. Smoking reduction fails to improve clinical and biological markers of cardiac disease: a randomized controlled trial. Nicotine Tob Res. [Randomized Controlled Trial

Research Support, N.I.H., Extramural]. 2008 Mar;10(3):471-81. doi: 10.1080/14622200801901948.

32. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. 2002 Mar 5;105(9):1135-43.

33. Ohsawa M, Okayama A, Nakamura M, Onoda T, Kato K, Itai K, Yoshida Y, Ogawa A, Kawamura K, Hiramori K. CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. Prev Med. [Research Support, Non-U.S. Gov't]. 2005 Aug;41(2):651-6.

34. Tracy RP, Kuller LH. C-reactive protein, heart disease risk, and the popular media. Arch Intern Med. [Comment Editorial Review]. 2005 Oct 10;165(18):2058-60.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

35. Tracy RP, Psaty BM, Macy E, Bovill EG, Cushman M, Cornell ES, Kuller LH. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. Arterioscler Thromb Vasc Biol. [Research Support, U.S. Gov't, P.H.S.]. 1997 Oct;17(10):2167-76.

36. Tuut M, Hense HW. Smoking, other risk factors and fibrinogen levels. evidence of effect modification. Ann Epidemiol2001 May;11(4):232-8.

37. Verma S, Yeh ET. C-reactive protein and atherothrombosis--beyond a biomarker: an actual partaker of lesion formation. Am J Physiol Regul Integr Comp Physiol. [Comment Review]. 2003 Nov;285(5):R1253-6; discussion R7-8.

38. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. Eur Heart J. [Multicenter Study Research Support, Non-U.S. Gov't]. 2005 Sep;26(17):1765-73. Epub 2005 Apr 7.

39. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. J Am Coll Cardiol. [Research Support, Non-U.S. Gov't Review]. 2007 May 29;49(21):2129-38. Epub 007 Apr 30.

40. Hemingway H, Philipson P, Chen R, Fitzpatrick NK, Damant J, Shipley M, Abrams KR, Moreno S, McAllister KS, Palmer S, Kaski JC, Timmis AD, Hingorani AD. Evaluating the quality of research into a single prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. PLoS Med. [Meta-Analysis Research Support, Non-U.S. Gov't Review]. 2010 Jun Jun 1;7(6):e1000286. doi: 10.1371/journal.pmed..

41. O'Callaghan PA, Fitzgerald A, Fogarty J, Gaffney P, Hanbidge M, Boran G, Enright H, Murphy J, McCarthy B, Graham IM. New and old cardiovascular risk factors: C-reactive protein, homocysteine, cysteine and von Willebrand factor increase risk, especially in smokers. Eur J Cardiovasc Prev Rehabil. [Comparative Study

Research Support, Non-U.S. Gov't]. 2005 Dec;12(6):542-7.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

42. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. Am J Epidemiol. [Multicenter Study

Research Support, U.S. Gov't, P.H.S.]. 1996 Sep 15;144(6):537-47.

43. Yosef-Levi IM, Grad E, Danenberg HD. [C-reactive protein and atherothrombosis--a prognostic factor or a risk factor?]. Harefuah. [Review]. 2007 Dec;2007 Dec;146(12):970-4.

44. Andreeva E, Melbye H. Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. BMC Fam Pract. [Randomized Controlled Trial]. 2014 May 2;15:80.(doi):10.1186/471-2296-15-80.

45. Cals JW, Ament AJ, Hood K, Butler CC, Hopstaken RM, Wassink GF, Dinant GJ. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. J Eval Clin Pract. [Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. 2011 Dec;17(6):1059-69. doi: 10.111/j.365-2753.010.01472.x. Epub 2010 Jul 8.

46. Cals JW, de Bock L, Beckers PJ, Francis NA, Hopstaken RM, Hood K, de Bont EG, Butler CC, Dinant GJ. Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. Ann Fam Med. [Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. 2013 Mar-Apr;11(2):157-64. doi: 10.1370/afm.477.

47. Engel MF, Paling FP, Hoepelman AI, van der Meer V, Oosterheert JJ. Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review. Fam Pract. [Review]. 2012 Aug;29(4):383-93. doi: 10.1093/fampra/cmr119. Epub 2011 Dec 8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

48. Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. Br J Gen Pract. [Meta-Analysis Review]. 2013 Nov;63(616):e787-94. doi: 10.3399/bjgp13X674477.

49. Kavanagh KE, O'Shea E, Halloran R, Cantillon P, Murphy AW. A pilot study of the use of near-patient C-Reactive Protein testing in the treatment of adult respiratory tract infections in one Irish general practice. BMC Fam Pract. [Research Support, Non-U.S. Gov't]. 2011 Aug 31;12:93.(doi):10.1186/471-2296-12-93.

50. Aksu F, Capan N, Aksu K, Ofluoglu R, Canbakan S, Yavuz B, Akin KO. C-reactive protein levels are raised in stable Chronic obstructive pulmonary disease patients independent of smoking behavior and biomass exposure. J Thorac Dis2013 Aug;5(4):414-21. doi: 10.3978/j.issn.2072-1439.2013.06.27.

51. Melbye H, Halvorsen DS, Hartz I, Medbo A, Brox J, Eggen AE, Njolstad I. Bronchial airflow limitation, smoking, body mass index, and statin use are strongly associated with the C-reactive protein level in the elderly. The Tromso Study 2001. Respir Med. [Research Support, Non-U.S. Gov't]. 2007 Dec;101(12):2541-9. Epub 007 Sep 6.

52. Pinto-Plata VM, Mullerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, Celli BR. C-reactive protein in patients with COPD, control smokers and non-smokers. Thorax. [Research Support, Non-U.S. Gov't]. 2006 Jan;61(1):23-8. Epub 2005 Sep 2.

53. Vaguliene N, Zemaitis M, Miliauskas S, Urboniene D, Sitkauskiene B, Sakalauskas R. Comparison of C-reactive protein levels in patients with lung cancer and chronic obstructive pulmonary disease. Medicina (Kaunas). [Comparative Study]. 2011;47(8):421-7. Epub 2011 Nov 18.

54. Gimeno D, Delclos GL, Ferrie JE, De Vogli R, Elovainio M, Marmot MG, Kivimaki M. Association of CRP and IL-6 with lung function in a middle-aged population initially free from self-reported respiratory problems: the Whitehall II study. Eur J Epidemiol. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2011 Feb;26(2):135-44. doi: 10.1007/s10654-010-9526-5. Epub 2011 Feb 4.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

55. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Crit Rev Clin Lab Sci. [Research Support, Non-U.S. Gov't Review]. 2011 Jul-Aug;48(4):155-70. doi: 10.3109/10408363.2011.599831.

56. Heikkila K, Silander K, Salomaa V, Jousilahti P, Koskinen S, Pukkala E, Perola M. C-reactive protein-associated genetic variants and cancer risk: findings from FINRISK 1992, FINRISK 1997 and Health 2000 studies. Eur J Cancer. [Multicenter Study Research Support, Non-U.S. Gov't]. 2011 Feb;47(3):404-12. doi: 10.1016/j.ejca.2010.07.032. Epub Aug 18.

57. Guo YZ, Pan L, Du CJ, Ren DQ, Xie XM. Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. Asian Pac J Cancer Prev. [Meta-Analysis]. 2013;14(1):243-8.

58. Ko YJ, Kwon YM, Kim KH, Choi HC, Chun SH, Yoon HJ, Goh E, Cho B, Park M. High-sensitivity C-reactive protein levels and cancer mortality. Cancer Epidemiol Biomarkers Prev2012 Nov;21(11):2076-86. doi: 10.1158/055-9965.EPI-12-0611.

59. Sin DD, Man SF, McWilliams A, Lam S. Progression of airway dysplasia and C-reactive protein in smokers at high risk of lung cancer. Am J Respir Crit Care Med. [Research Support, N.I.H., Extramural

Research Support, Non-U.S. Gov't]. 2006 Mar 1;173(5):535-9. Epub 2005 Dec 9.

60. Alifano M, Falcoz PE, Seegers V, Roche N, Schussler O, Younes M, Antonacci F, Forgez P, Dechartres A, Massard G, Damotte D, Regnard JF. Preresection serum C-reactive protein measurement and survival among patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg. [Multicenter Study]. 2011 Nov;142(5):1161-7. doi: 10.016/j.jtcvs.2011.07.021. Epub Aug 26.

61. Hong S, Kang YA, Cho BC, Kim DJ. Elevated serum C-reactive protein as a prognostic marker in small cell lung cancer. Yonsei Med J. [Research Support, Non-U.S. Gov't]. 2012 Jan;53(1):111-7. doi: 10.3349/ymj.2012.53.1.111.

62. Kanoh Y, Abe T, Masuda N, Akahoshi T. Progression of non-small cell lung cancer: diagnostic and prognostic utility of matrix metalloproteinase-2, C-reactive protein and serum amyloid A. Oncol Rep. [Research Support, Non-U.S. Gov't]. 2013 Feb;29(2):469-73. doi: 10.3892/or.2012.123. Epub Nov 5.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

63. Allin KH, Bojesen SE, Johansen JS, Nordestgaard BG. Cancer risk by combined levels of YKL-40 and C-reactive protein in the general population. Br J Cancer2012 Jan 3;106(1):199-205. doi: 10.1038/bjc.2011.501. Epub Nov 17.

64. Pine SR, Mechanic LE, Enewold L, Chaturvedi AK, Katki HA, Zheng YL, Bowman ED, Engels EA, Caporaso NE, Harris CC. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. J Natl Cancer Inst. [Research Support, N.I.H., Intramural]. 2011 Jul 20;103(14):1112-22. doi: 10.093/jnci/djr216. Epub 2011 Jun 17.

65. Zhou B, Liu J, Wang ZM, Xi T. C-reactive protein, interleukin 6 and lung cancer risk: a meta-analysis. PLoS One. [Meta-Analysis]. 2012;7(8):e43075. doi: 10.1371/journal.pone.0043075. Epub 2012 Aug 17.

66. Lukaszewicz-Zajac M, Mroczko B, Szmitkowski M. [The role of interleukin-6 and C-reactive protein in gastric cancer]. Pol Merkur Lekarski. [Review]. 2010 Dec;29(174):382-6.

67. Douglas JB, Silverman DT, Weinstein SJ, Graubard BI, Pollak MN, Tao Y, Virtamo J, Albanes D, Stolzenberg-Solomon RZ. Serum C-reactive protein and risk of pancreatic cancer in two nested, case-control studies. Cancer Epidemiol Biomarkers Prev. [Comparative Study Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Intramural]. 2011 Feb;20(2):359-69. doi: 10.1158/055-9965.EPI-10-1024. Epub 2010 Dec 20.

68. Kruse AL, Luebbers HT, Gratz KW. C-reactive protein levels: a prognostic marker for patients with head and neck cancer? Head Neck Oncol2010 Aug 2;2:21.(doi):10.1186/758-3284-2-21.

69. Hanyu O, Yoshida J, Abe E, Hirayama S, Miyake K, Aizawa Y, Miida T. High-sensitivity CRP reflects insulin resistance in smokers. J Atheroscler Thromb. [Research Support, Non-U.S. Gov't]. 2009 Oct;16(5):560-7. Epub 2009 Sep 14.

70. Madsen C, Nafstad P, Eikvar L, Schwarze PE, Ronningen KS, Haaheim LL. Association between tobacco smoke exposure and levels of C-reactive protein in the Oslo II Study. Eur J Epidemiol. [Research Support, Non-U.S. Gov't]. 2007;22(5):311-7. Epub 2007 May 5.

71. Ahonen TM, Kautiainen HJ, Keinanen-Kiukaanniemi SM, Kumpusalo EA, Vanhala MJ. Gender difference among smoking, adiponectin, and high-sensitivity C-reactive protein. Am J Prev Med. [Comparative Study]. 2008 Dec;35(6):598-601. doi: 10.1016/j.amepre.2008.09.011. Epub Oct 8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

72. Kleber ME, Siekmeier R, Delgado G, Grammer TB, Winkelmann BR, Scharnagl H, Boehm BO, Marz W. C-reactive protein and lipoprotein-associated phospholipase A2 in smokers and nonsmokers of the Ludwigshafen Risk and Cardiovascular Health study. Adv Exp Med Biol. [Research Support, Non-U.S. Gov't]. 2015;832:15-23.(doi):10.1007/5584_2014_6.

73. Mao J, Liu J, Pang X, Li M, Song J, Han C, Wu D, Wang S. Nicotine induces the expression of C-reactive protein via MAPK-dependent signal pathway in U937 macrophages. Mol Cells. [Research Support, Non-U.S. Gov't]. 2012 Nov;34(5):457-61. doi: 10.1007/s10059-012-0205-0. Epub 2012 Nov 6.

74. Ohsawa M, Itai K, Onoda T, Tanno K, Sasaki S, Nakamura M, Ogawa A, Sakata K, Kawamura K, Kuribayashi T, Yoshida Y, Okayama A. Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers. Atherosclerosis. [Research Support, Non-U.S. Gov't]. 2008 Nov;201(1):184-91. doi: 10.1016/j.atherosclerosis.2008.01.008. Epub Mar 17.

75. Frohlich M, Sund M, Lowel H, Imhof A, Hoffmeister A, Koenig W. Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). Eur Heart J2003 Jul;24(14):1365-72.

76. Helmersson J, Larsson A, Vessby B, Basu S. Active smoking and a history of smoking are associated with enhanced prostaglandin F(2alpha), interleukin-6 and F2-isoprostane formation in elderly men. Atherosclerosis. [Research Support, Non-U.S. Gov't]. 2005 Jul;181(1):201-7. Epub 2005 Apr 26.

77. Lowe GD, Yarnell JW, Rumley A, Bainton D, Sweetnam PM. C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis? Arterioscler Thromb Vasc Biol. [Research Support, Non-U.S. Gov't]. 2001 Apr;21(4):603-10.

78. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. Ann Intern Med. [Research Support, U.S. Gov't, P.H.S.]. 2003 Jun 3;138(11):891-7.

79. Panagiotakos DB, Pitsavos C, Chrysohoou C, Skoumas J, Masoura C, Toutouzas P, Stefanadis C. Effect of exposure to secondhand smoke on markers of inflammation: the ATTICA study. Am J Med2004 Feb 1;116(3):145-50.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

80. Garcia-Lorda P, Bullo M, Balanza R, Salas-Salvado J. C-reactive protein, adiposity and cardiovascular risk factors in a Mediterranean population. Int J Obes (Lond). [Research Support, Non-U.S. Gov't]. 2006 Mar;30(3):468-74.

81. Dietrich T, Garcia RI, de Pablo P, Schulze PC, Hoffmann K. The effects of cigarette smoking on C-reactive protein concentrations in men and women and its modification by exogenous oral hormones in women. Eur J Cardiovasc Prev Rehabil. [Research Support, N.I.H., Extramural]. 2007 Oct;14(5):694-700.

82. Saijo Y, Yoshioka E, Fukui T, Kawaharada M, Sata F, Sato H, Kishi R. Effects of the Interaction between Interleukin-6 -634C/G Polymorphism and Smoking on Serum C-Reactive Protein Concentrations. Hypertens Res. [Research Support, Non-U.S. Gov't]. 2007 Jul;30(7):593-9.

83. Levitzky YS, Guo CY, Rong J, Larson MG, Walter RE, Keaney JF, Jr., Sutherland PA, Vasan A, Lipinska I, Evans JC, Benjamin EJ. Relation of smoking status to a panel of inflammatory markers: the framingham offspring. Atherosclerosis. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2008 Nov;201(1):217-24. doi: 10.1016/j.atherosclerosis.2007.12.058. Epub 8 Mar 4.

84. Hastie CE, Haw S, Pell JP. Impact of smoking cessation and lifetime exposure on C-reactive protein. Nicotine Tob Res2008 Apr;10(4):637-42. doi: 10.1080/14622200801978722.

85. O'Loughlin J, Lambert M, Karp I, McGrath J, Gray-Donald K, Barnett TA, Delvin EE, Levy E, Paradis G. Association between cigarette smoking and C-reactive protein in a representative, population-based sample of adolescents. Nicotine Tob Res. [Research Support, Non-U.S. Gov't]. 2008 Mar;10(3):525-32. doi: 10.1080/14622200801901997.

86. Calapai G, Caputi AP, Mannucci C, Gregg EO, Pieratti A, Aurora RG, Chaudhary N, Puntoni R, Lowe F, McEwan M, Bassi A, Morandi S, Nunziata A. A cross-sectional investigation of biomarkers of risk after a decade of smoking. InhalToxicol2009 11/2009;21(13):1138-43.

87. Azar R, Richard A. Elevated salivary C-reactive protein levels are associated with active and passive smoking in healthy youth: A pilot study. J Inflamm (Lond)2011 Dec 7;8(1):37. doi: 10.1186/476-9255-8-37.

88. Frost-Pineda K, Liang Q, Liu J, Rimmer L, Jin Y, Feng S, Kapur S, Mendes P, Roethig H, Sarkar M. Biomarkers of Potential Harm Among Adult Smokers and Nonsmokers in the Total Exposure Study. NicotineTobRes2011 2/3/2011;13(3):182-93.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

89. Le-Ha C, Beilin LJ, Burrows S, Oddy WH, Hands B, Mori TA. Gender and the active smoking and high-sensitivity C-reactive protein relation in late adolescence. J Lipid Res. [Research Support, Non-U.S. Gov't]. 2014 Apr;55(4):758-64. doi: 10.1194/jlr.P045369. Epub 2014 Feb 27.

90. Khand F, Shaikh SS, Ata MA, Shaikh SS. Evaluation of the effect of smoking on complete blood counts, serum C-reactive protein and magnesium levels in healthy adult male smokers. J Pak Med Assoc. [Research Support, Non-U.S. Gov't]. 2015 Jan;65(1):59-61.

91. Kawada T. Relationships between the smoking status and plasma fibrinogen, white blood cell count and serum C-reactive protein in Japanese workers. Diabetes Metab Syndr. [Journal article]. 2015 Mar 6;6(15):00023-5.

92. Kiechl S, Werner P, Egger G, Oberhollenzer F, Mayr M, Xu Q, Poewe W, Willeit J. Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. Stroke2002 Sep;33(9):2170-6.

93. Merghani TH, Saeed A, Alawad A. Changes in plasma IL4, TNFa and CRP in response to regular passive smoking at home among healthy school children in Khartoum, Sudan. Afr Health Sci2012 Mar;12(1):41-7.

94. Alyan O, Kacmaz F, Ozdemir O, Karahan Z, Taskesen T, Iyem H, Alan S, Karadede A, Ilkay E. [High levels of high-sensitivity C-reactive protein and impaired autonomic activity in smokers]. Turk Kardiyol Dern Ars2008 Sep;36(6):368-75.

95. Feng D, Liu T, Wang H, Karp E, Ling W, Chen WQ. Mediation role of C-reactive protein on the association between smoking quantity and type 2 diabetes in current Chinese smokers. J Diabetes Res. [Multicenter Study]. 2014;2014:171538.(doi):10.1155/2014/171538. Epub 2014 Jul 3.

96. Crook MA, Scott DA, Stapleton JA, Palmer RM, Wilson RF, Sutherland G. Circulating concentrations of C-reactive protein and total sialic acid in tobacco smokers remain unchanged following one year of validated smoking cessation. Eur J Clin Invest2000 Oct;30(10):861-5.

97. Rohde LE, Hennekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. Am J Cardiol. [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 1999 Nov 1;84(9):1018-22.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

98. Martin de Diego CE, Gomez de Terreros Sanchez FJ, Caro de Miguel MC, Medina Font J, Matesanz Ruiz C, Gomez de Terreros Caro J. [C-reactive protein value related to a smoking history and composition of nicotine and tobacco tar]. An Med Interna2006 Jan;23(1):3-10.

99. Roethig HJ, Feng S, Liang Q, Liu J, Rees WA, Zedler BK. A 12-Month, Randomized, Controlled Study to Evaluate Exposure and Cardiovascular Risk Factors in Adult Smokers Switching From Conventional Cigarettes to a Second-Generation Electrically Heated Cigarette Smoking System. JClinPharmacol2008 3/4/2008;48:580-91.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7 APPENDICES

7.1 Appendix 1 References related to the included studies (reference number in brackets)

7.2 Appendix 2 Inclusion criteria A

7.3 Appendix 3 Inclusion criteria B

7.4 Appendix 4 Inclusion criteria C

7.5 Appendix 5 Inclusion criteria D

7.6 Appendix 6 Inclusion criteria E

7.7 Appendix 7 Inclusion criteria F

7.8 Appendix 8 Inclusion criteria G

7.9 Appendix 9 Review articles

7.10 Appendix 10 Excluded articles

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.1 Appendix 1 References of included studies (reference number in brackets)

Articles were assigned (included, excluded) according the following criteria

0x Excluded (not belonging to at least one category A - G or R)

A Association to CVD

B Association to respiratory diseases

C Association to other diseases

D Levels in smokers and non-smokers

E Dose-response relationship to smoking intensity

F Effect of smoking cessation

G Effect of switching to MRTPs or other nicotine products

R Review article

Articles were included, if they provide relevant information on the criteria A – G or were assigned as relevant review for the biomarker of interest. All other articles are excluded from the evaluation (assigned as 0x, x (reason for exclusion) = 1 to 5).

01 No usable data or information on CRP were presented

02 Clinical study with patients, focus on diagnosis, therapy and prognosis

03 Population investigated is not relevant for the purpose of this document (e.g. children, pregnant women, ill persons)

04 The topic investigated is not relevant for smoking or a smoking-related disease

05 Animal or *in vitro* studies with no obvious relation to humans

Sources for published articles to be used for generation of the document

Source 1: Two monographs on biomarkers of effect and smoking [1, 2]

Source 2: Articles derived from monographs: 22 References [3-24]

Source 3: Articles from PubMed Search 1 (Reviews on CRP): 14 References [25-38]

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Source 4: Articles derived from PubMed Search 2 (smoking-related studies on CRP: 43 References [15, 37, 39-79]

Source 5: Articles derived from PubMed Search 3 (association between CRP and cardiovascular diseases): 25 References [80-104]

Source 6: Articles derived from PubMed Search 4 (association between CRP and respiratory diseases): 17 References [105-121]

Source 7: Articles derived from PubMed Search 4 (association between CRP and cancer): 26 References [122-147]

Source 8: Articles derived from citations in publications from Sources 2 - 7: 21 References [148-168]

References of all retrieved articles

(1) Life Sciences Research Office (LSRO). (2007) *Biological effects assessment in the evaluation of potential reduced-risk tobacco products*. Bethesda, Maryland, USA. **R, A, D, E, F**

(2) US Department of Health and Human Services. (2010) *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*

A Report of the Surgeon General. **R, A, D, F**

(3) Axelsson, T., Jansson, P. A., Smith, U., and Eliasson, B. (2001) Nicotine infusion acutely impairs insulin sensitivity in type 2 diabetic patients but not in healthy subjects. *J Intern Med.*, *249*, 539-544. **01**

(4) Bakhru, A., and Erlinger, T. P. (2005) Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. *PLoS Med.*, *2*, e160. Epub 2005 Jun 2028. **D, E, F**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(5) Benowitz, N. L., Fitzgerald, G. A., Wilson, M., and Zhang, Q. (1993) Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. *Journal of the American College of Cardiology*, *22*, 1159-1167. **D, G**

(6) Blaschke, F., Bruemmer, D., Yin, F., Takata, Y., Wang, W., Fishbein, M. C., Okura, T., Higaki, J., Graf, K., Fleck, E., Hsueh, W. A., and Law, R. E. (2004) C-reactive protein induces apoptosis in human coronary vascular smooth muscle cells. *Circulation.*, *110*, 579-587. Epub 2004 Jul 2026. **A**

(7) Burke, A. P., Tracy, R. P., Kolodgie, F., Malcom, G. T., Zieske, A., Kutys, R., Pestaner, J., Smialek, J., and Virmani, R. (2002) Elevated C-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies. *Circulation.*, *105*, 2019-2023. **A**

(8) Chakraborti, T., Mandal, A., Mandal, M., Das, S., and Chakraborti, S. (2000) Complement activation in heart diseases. Role of oxidants. *Cell Signal.*, *12*, 607-617. **02**

(9) Danesh, J., Wheeler, J. G., Hirschfield, G. M., Eda, S., Eiriksdottir, G., Rumley, A., Lowe, G. D., Pepys, M. B., and Gudnason, V. (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med.*, *350*, 1387-1397. **A**

(10) Fu, T., and Borensztajn, J. (2002) Macrophage uptake of low-density lipoprotein bound to aggregated C-reactive protein: possible mechanism of foam-cell formation in atherosclerotic lesions. *Biochem J.*, *366*, 195-201. **A**

(11) Jensen, E. J., Pedersen, B., Frederiksen, R., and Dahl, R. (1998) Prospective study on the effect of smoking and nicotine substitution on leucocyte blood counts and relation between blood leucocytes and lung function. *Thorax.*, *53*, 784-789. **01**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(12) Joseph, A. M., Hecht, S. S., Murphy, S. E., Carmella, S. G., Le, C. T., Zhang, Y., Han, S., and Hatsukami, D. K. (2005) Relationships between cigarette consumption and biomarkers of tobacco toxin exposure. *Cancer Epidemiol Biomarkers Prev.*, *14*, 2963-2968. **01**

(13) Joseph, A. M., Hecht, S. S., Murphy, S. E., Lando, H., Carmella, S. G., Gross, M., Bliss, R., Le, C. T., and Hatsukami, D. K. (2008) Smoking reduction fails to improve clinical and biological markers of cardiac disease: a randomized controlled trial. *Nicotine Tob Res.*, *10*, 471-481. doi: 410.1080/14622200801901948. **D, E, F**

(14) Libby, P., Ridker, P. M., and Maseri, A. (2002) Inflammation and atherosclerosis. *Circulation.*, *105*, 1135-1143. **A**

(15) Ohsawa, M., Okayama, A., Nakamura, M., Onoda, T., Kato, K., Itai, K., Yoshida, Y., Ogawa, A., Kawamura, K., and Hiramori, K. (2005) CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. *Prev Med.*, *41*, 651-656. **D, E, F**

(16) Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., 3rd, Criqui, M., Fadl, Y. Y., Fortmann, S. P., Hong, Y., Myers, G. L., Rifai, N., Smith, S. C., Jr., Taubert, K., Tracy, R. P., and Vinicor, F. (2003) Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.*, *107*, 499-511. **A**

(17) Rackley, C. E. (2004) New clinical markers predictive of cardiovascular disease: the role of inflammatory mediators. *Cardiol Rev.*, *12*, 151-157. **A**

(18) Ridker, P. M., Brown, N. J., Vaughan, D. E., Harrison, D. G., and Mehta, J. L. (2004) Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation.*, *109*, IV6-19. **A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(19) Tracy, R. P., and Kuller, L. H. (2005) C-reactive protein, heart disease risk, and the popular media. *Arch Intern Med.*, *165*, 2058-2060. **A**

(20) Tracy, R. P., Psaty, B. M., Macy, E., Bovill, E. G., Cushman, M., Cornell, E. S., and Kuller, L. H. (1997) Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol.*, *17*, 2167-2176. **D, E, F**

(21) Tuut, M., and Hense, H. W. (2001) Smoking, other risk factors and fibrinogen levels. evidence of effect modification. *Ann Epidemiol.*, *11*, 232-238. **01**

(22) Verma, S., and Yeh, E. T. (2003) C-reactive protein and atherothrombosis--beyond a biomarker: an actual partaker of lesion formation. *Am J Physiol Regul Integr Comp Physiol.*, *285*, R1253-1256; discussion R1257-1258. **A**

(23) Vigushin, D. M., Pepys, M. B., and Hawkins, P. N. (1993) Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. *J Clin Invest.*, *91*, 1351-1357. **A**

(24) Wannamethee, S. G., Lowe, G. D., Shaper, A. G., Rumley, A., Lennon, L., and Whincup, P. H. (2005) Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur Heart J.*, *26*, 1765-1773. Epub 2005 Apr 1767. **D**

(25) Corrado, E., and Novo, S. (2007) [High sensitivity of C-reactive protein in primary prevention]. *G Ital Cardiol (Rome). 8*, 327-334. **R, A**

(26) Fabijanic, D., Banic, M., and Kardum, D. (2006) [C-reactive protein in cardiovascular risk evaluation]. *Lijec Vjesn.*, *128*, 167-174. **R, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(27) Hemingway, H., Philipson, P., Chen, R., Fitzpatrick, N. K., Damant, J., Shipley, M., Abrams, K. R., Moreno, S., McAllister, K. S., Palmer, S., Kaski, J. C., Timmis, A. D., and Hingorani, A. D. (2010) Evaluating the quality of research into a single prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. *PLoS Med.*, *7*, e1000286. doi: 1000210.1001371/journal.pmed.1000286. **R, A**

(28) Kao, P. C., Shiesh, S. C., and Wu, T. J. (2006) Serum C-reactive protein as a marker for wellness assessment. *Ann Clin Lab Sci.*, *36*, 163-169. **R, A**

(29) Miller, B. J., Culpepper, N., and Rapaport, M. H. (2014) C-reactive protein levels in schizophrenia: a review and meta-analysis. *Clin Schizophr Relat Psychoses.*, *7*, 223-230. doi: 210.3371/CSRP.MICU.020813. **R, C**

(30) Nanri, A., Moore, M. A., and Kono, S. (2007) Impact of C-reactive protein on disease risk and its relation to dietary factors. *Asian Pac J Cancer Prev.*, *8*, 167-177. **R**

(31) Plaisance, E. P., and Grandjean, P. W. (2006) Physical activity and high-sensitivity C-reactive protein. *Sports Med*, *36*, 443-458. **R**

(32) Ridker, P. M. (2007) C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol.*, *49*, 2129-2138. Epub 2007 Apr 2130. **R, A**

(33) Ridker, P. M., and Silvertown, J. D. (2008) Inflammation, C-reactive protein, and atherothrombosis. *J Periodontol.*, *79*, 1544-1551. doi: 1510.1902/jop.2008.080249. **R, A**

(34) Rodrigues, I. M., and Klein, L. C. (2006) Boiled or filtered coffee? Effects of coffee and caffeine on cholesterol, fibrinogen and C-reactive protein. *Toxicol Rev*, *25*, 55-69. **R, A**

(35) Rudolf, J., and Lewandrowski, K. B. (2014) Cholesterol, lipoproteins, high-sensitivity c-reactive protein, and other risk factors for atherosclerosis. *Clin Lab Med*, *2014 Mar;34*, 113-127. **R, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(36) Shah, T., Newcombe, P., Smeeth, L., Addo, J., Casas, J. P., Whittaker, J., Miller, M. A., Tinworth, L., Jeffery, S., Strazzullo, P., Cappuccio, F. P., and Hingorani, A. D. (2010) Ancestry as a determinant of mean population C-reactive protein values: implications for cardiovascular risk prediction. *Circ Cardiovasc Genet.*, *3*, 436-444. doi: 410.1161/CIRCGENETICS.1110.957431. Epub 952010 Sep 957428. **R**

(37) Tonstad, S., and Cowan, J. L. (2009) C-reactive protein as a predictor of disease in smokers and former smokers: a review. *Int J Clin Pract.*, *63*, 1634-1641. doi: 1610.1111/j.1742-1241.2009.02179.x. Epub 02009 Aug 02129. **R, A, C, D, E, F**

(38) Yosef-Levi, I. M., Grad, E., and Danenberg, H. D. (2007) [C-reactive protein and atherothrombosis--a prognostic factor or a risk factor?]. *Harefuah*, *2007 Dec;146*, 970-974. **R, A**

(39) Ahonen, T. M., Kautiainen, H. J., Keinanen-Kiukaanniemi, S. M., Kumpusalo, E. A., and Vanhala, M. J. (2008) Gender difference among smoking, adiponectin, and high-sensitivity C-reactive protein. *Am J Prev Med.*, *35*, 598-601. doi: 510.1016/j.amepre.2008.1009.1011. Epub 2008 Oct 1018. **D, E, F, A**

(40) Aksu, F., Capan, N., Aksu, K., Ofluoglu, R., Canbakan, S., Yavuz, B., and Akin, K. O. (2013) C-reactive protein levels are raised in stable Chronic obstructive pulmonary disease patients independent of smoking behavior and biomass exposure. *J Thorac Dis.*, *5*, 414-421. doi: 410.3978/j.issn.2072-1439.2013.3906.3927. **D, B**

(41) Alshaarawy, O., and Anthony, J. C. (2015) Cannabis smoking and serum C-reactive protein: a quantile regressions approach based on NHANES 2005-2010. *Drug Alcohol Depend.*, *147:203-7.*, 10.1016/j.drugalcdep.2014.1011.1017. Epub 2014 Nov 1028. **04**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(42) Alyan, O., Kacmaz, F., Ozdemir, O., Karahan, Z., Taskesen, T., Iyem, H., Alan, S., Karadede, A., and Ilkay, E. (2008) [High levels of high-sensitivity C-reactive protein and impaired autonomic activity in smokers]. *Turk Kardiyol Dern Ars.*, *36*, 368-375. **D, E**

(43) Azar, R., and Richard, A. (2011) Elevated salivary C-reactive protein levels are associated with active and passive smoking in healthy youth: A pilot study. *J Inflamm (Lond). 8*, 37. doi: 10.1186/1476-9255-1188-1137. **D, E**

(44) Cupul-Uicab, L. A., Skjaerven, R., Haug, K., Travlos, G. S., Wilson, R. E., Eggesbo, M., Hoppin, J. A., Whitworth, K. W., and Longnecker, M. P. (2012) Exposure to tobacco smoke in utero and subsequent plasma lipids, ApoB, and CRP among adult women in the MoBa cohort. *Environ Health Perspect.*, *120*, 1532-1537. doi: 1510.1289/ehp.1104563. Epub 1102012 Jul 1104519. **03**

(45) Dietrich, T., Garcia, R. I., de Pablo, P., Schulze, P. C., and Hoffmann, K. (2007) The effects of cigarette smoking on C-reactive protein concentrations in men and women and its modification by exogenous oral hormones in women. *Eur J Cardiovasc Prev Rehabil.*, *14*, 694-700. **D, E, F**

(46) El Safoury, O. S., Ezzat, M., Abdelhamid, M. F., Shoukry, N., and Badawy, E. (2013) The Evaluation of the Impact of Age, Skin Tags, Metabolic Syndrome, Body Mass Index, and Smoking on Homocysteine, Endothelin-1, High-sensitive C-reactive Protein, and on the Heart. *Indian J Dermatol.*, *58*, 326. doi: 310.4103/0019-5154.113947. **03**

(47) Fagerberg, B., Behre, C. J., Wikstrand, J., Hulten, L. M., and Hulthe, J. (2008) C-reactive protein and tumor necrosis factor-alpha in relation to insulin-mediated glucose uptake, smoking and atherosclerosis. *Scand J Clin Lab Invest*, *68*, 534-541. doi: 510.1080/00365510701870898. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(48) Feng, D., Liu, T., Wang, H., Karp, E., Ling, W., and Chen, W. Q. (2014) Mediation role of C-reactive protein on the association between smoking quantity and type 2 diabetes in current Chinese smokers. *J Diabetes Res*, *2014:171538.*, 10.1155/2014/171538. Epub 172014 Jul 171533. **D, E**

(49) Hanyu, O., Yoshida, J., Abe, E., Hirayama, S., Miyake, K., Aizawa, Y., and Miida, T. (2009) High-sensitivity CRP reflects insulin resistance in smokers. *J Atheroscler Thromb.*, *16*, 560-567. Epub 2009 Sep 2014. **D**

(50) Hastie, C. E., Haw, S., and Pell, J. P. (2008) Impact of smoking cessation and lifetime exposure on C-reactive protein. *Nicotine Tob Res.*, *10*, 637-642. doi: 610.1080/14622200801978722. **D, E, F**

(51) Hatzis, G., Tousoulis, D., Papageorgiou, N., Bouras, G., Oikonomou, E., Miliou, A., Siasos, G., Toutouzas, K., Papaioannou, S., Tsiamis, E., Antoniades, C., and Stefanadis, C. (2014) Combined effects of smoking and interleukin-6 and C-reactive protein genetic variants on endothelial function, inflammation, thrombosis and incidence of coronary artery disease. *Int J Cardiol.*, *176*, 254-257. doi: 210.1016/j.ijcard.2014.1006.1058. Epub 2014 Jul 1015. **03**

(52) Hilawe, E. H., Yatsuya, H., Li, Y., Uemura, M., Wang, C., Chiang, C., Toyoshima, H., Tamakoshi, K., Zhang, Y., Kawazoe, N., and Aoyama, A. (2015) Smoking and diabetes: is the association mediated by adiponectin, leptin, or C-reactive protein? *J Epidemiol*, *25*, 99-109. doi: 110.2188/jea.JE20140055. Epub 20142014 Nov 20140015. **03**

(53) Hung, M. Y., Hsu, K. H., Hung, M. J., Cheng, C. W., Kuo, L. T., and Cherng, W. J. (2009) Interaction between cigarette smoking and high-sensitivity C-reactive protein in the development of coronary vasospasm in patients without hemodynamically significant coronary artery disease. *Am J Med Sci.*, *338*, 440-446. doi: 410.1097/MAJ.1090b1013e3181b9147f. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(54) Kawada, T. (2015) Relationships between the smoking status and plasma fibrinogen, white blood cell count and serum C-reactive protein in Japanese workers. *Diabetes Metab Syndr*, *6*, 00023-00025. **D, E, F**

(55) Khand, F., Shaikh, S. S., Ata, M. A., and Shaikh, S. S. (2015) Evaluation of the effect of smoking on complete blood counts, serum C-reactive protein and magnesium levels in healthy adult male smokers. *J Pak Med Assoc.*, *65*, 59-61. **D**

(56) Khoo, C. M., Tan, M., Wu, Y., Wai, C. H., Subramaniam, T., Lee, J., and Tai, E. S. (2011) Central obesity and smoking are key modifiable risk factors for elevated C-reactive protein in Asian individuals who are not eligible for statin therapy. *Nutr Diabetes.*, *1:e8.*, 10.1038/nutd.2011.1034. **D, F**

(57) Kleber, M. E., Siekmeier, R., Delgado, G., Grammer, T. B., Winkelmann, B. R., Scharnagl, H., Boehm, B. O., and Marz, W. (2015) C-reactive protein and lipoprotein-associated phospholipase A2 in smokers and nonsmokers of the Ludwigshafen Risk and Cardiovascular Health study. *Adv Exp Med Biol*, *832:15-23.*, 10.1007/5584_2014_1006. **D**

(58) Koch, A., Fohlin, H., and Sorenson, S. (2009) Prognostic significance of C-reactive protein and smoking in patients with advanced non-small cell lung cancer treated with first-line palliative chemotherapy. *J Thorac Oncol.*, *4*, 326-332. doi: 310.1097/JTO.1090b1013e31819578c31819578. **D, C**

(59) Kodovazenitis, G., Pitsavos, C., Papadimitriou, L., Deliargyris, E. N., Vrotsos, I., Stefanadis, C., and Madianos, P. N. (2011) Periodontal disease is associated with higher levels of C-reactive protein in non-diabetic, non-smoking acute myocardial infarction patients. *J Dent.*, *39*, 849-854. doi: 810.1016/j.jdent.2011.1009.1005. Epub 2011 Sep 1017. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(60) Krintus, M., Sypniewska, G., and Kuligowska-Prusinska, M. (2010) Effect of second and third generation oral contraceptives on C-reactive protein, lipids and apolipoproteins in young, non-obese, non-smoking apparently healthy women. *Clin Biochem.*, *43*, 626-628. doi: 610.1016/j.clinbiochem.2009.1012.1013. Epub 2009 Dec 1021. **04**

(61) Le-Ha, C., Beilin, L. J., Burrows, S., Oddy, W. H., Hands, B., and Mori, T. A. (2014) Gender and the active smoking and high-sensitivity C-reactive protein relation in late adolescence. *J Lipid Res.*, *55*, 758-764. doi: 710.1194/jlr.P045369. Epub 042014 Feb 045327. **D**

(62) Lopez-Campos, J. L., Montes-Worboys, A., Calero, C., Marquez-Martin, E., Cejudo, P., Ortega, F., and Arellano, E. (2012) Cyclooxygenase-2 -765G>C polymorphism is associated with C-reactive protein levels in resistant smokers but not in chronic obstructive pulmonary disease patients. *Respir Physiol Neurobiol.*, *180*, 119-125. doi: 110.1016/j.resp.2011.1011.1001. Epub 2011 Nov 1019. **03**

(63) Madsen, C., Nafstad, P., Eikvar, L., Schwarze, P. E., Ronningen, K. S., and Haaheim, L. L. (2007) Association between tobacco smoke exposure and levels of C-reactive protein in the Oslo II Study. *Eur J Epidemiol*, *22*, 311-317. Epub 2007 May 2005. **D, E, F**

(64) Mao, J., Liu, J., Pang, X., Li, M., Song, J., Han, C., Wu, D., and Wang, S. (2012) Nicotine induces the expression of C-reactive protein via MAPK-dependent signal pathway in U937 macrophages. *Mol Cells.*, *34*, 457-461. doi: 410.1007/s10059-10012-10205-10050. Epub 12012 Nov 10056. **D**

(65) Martin de Diego, C. E., Gomez de Terreros Sanchez, F. J., Caro de Miguel, M. C., Medina Font, J., Matesanz Ruiz, C., and Gomez de Terreros Caro, J. (2006) [C-reactive protein value related to a smoking history and composition of nicotine and tobacco tar]. *An Med Interna.*, *23*, 3-10. **D, E, F**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(66) Melbye, H., Halvorsen, D. S., Hartz, I., Medbo, A., Brox, J., Eggen, A. E., and Njolstad, I. (2007) Bronchial airflow limitation, smoking, body mass index, and statin use are strongly associated with the C-reactive protein level in the elderly. The Tromso Study 2001. *Respir Med.*, *101*, 2541-2549. Epub 2007 Sep 2546. **D, B**

(67) Merghani, T. H., Saeed, A., and Alawad, A. (2012) Changes in plasma IL4, TNFa and CRP in response to regular passive smoking at home among healthy school children in Khartoum, Sudan. *Afr Health Sci.*, *12*, 41-47. **D**

(68) Moghbeli, N., Kirtane, A. J., Ray, K. K., Murphy, S. A., Gibson, C. M., Braunwald, E., and Cannon, C. P. (2005) C-reactive protein and cardiovascular outcomes in smokers versus nonsmokers in non-ST-elevation acute coronary syndrome (from the TACTICS-TIMI 18 trial). *Am J Cardiol.*, *96*, 635-638. **03**

(69) O'Callaghan, P. A., Fitzgerald, A., Fogarty, J., Gaffney, P., Hanbidge, M., Boran, G., Enright, H., Murphy, J., McCarthy, B., and Graham, I. M. (2005) New and old cardiovascular risk factors: C-reactive protein, homocysteine, cysteine and von Willebrand factor increase risk, especially in smokers. *Eur J Cardiovasc Prev Rehabil.*, *12*, 542-547. **D, A**

(70) Ohsawa, M., Itai, K., Onoda, T., Tanno, K., Sasaki, S., Nakamura, M., Ogawa, A., Sakata, K., Kawamura, K., Kuribayashi, T., Yoshida, Y., and Okayama, A. (2008) Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers. *Atherosclerosis.*, *201*, 184-191. doi: 110.1016/j.atherosclerosis.2008.1001.1008. Epub 2008 Mar 1017. **D**

(71) O'Loughlin, J., Lambert, M., Karp, I., McGrath, J., Gray-Donald, K., Barnett, T. A., Delvin, E. E., Levy, E., and Paradis, G. (2008) Association between cigarette smoking and C-reactive protein in a representative, population-based sample of adolescents. *Nicotine Tob Res.*, *10*, 525-532. doi: 510.1080/14622200801901997. **D, E**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(72) Pinto-Plata, V. M., Mullerova, H., Toso, J. F., Feudjo-Tepie, M., Soriano, J. B., Vessey, R. S., and Celli, B. R. (2006) C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax.*, *61*, 23-28. Epub 2005 Sep 2002. **D, B**

(73) Saijo, Y., Yoshioka, E., Fukui, T., Kawaharada, M., Sata, F., Sato, H., and Kishi, R. (2007) Effects of the Interaction between Interleukin-6 -634C/G Polymorphism and Smoking on Serum C-Reactive Protein Concentrations. *Hypertens Res.*, *30*, 593-599.

(74) Sauriasari, R., Sakano, N., Wang, D. H., Takaki, J., Takemoto, K., Wang, B., **D** Sugiyama, H., Sato, Y., Takigawa, T., Takahashi, N., Kanbara, S., Hitomi, Y., Nakamura, H., and Ogino, K. (2010) C-reactive protein is associated with cigarette smoking-induced hyperfiltration and proteinuria in an apparently healthy population. *Hypertens Res.*, *33*, 1129-1136. doi: 1110.1038/hr.2010.1154. Epub 2010 Aug 1112. **02**

(75) Siedlinski, M., Klanderman, B., Sandhaus, R. A., Barker, A. F., Brantly, M. L., Eden, E., McElvaney, N. G., Rennard, S. I., Stocks, J. M., Stoller, J. K., Strange, C., Turino, G. M., Campbell, E. J., and Demeo, D. L. (2012) Association of cigarette smoking and CRP levels with DNA methylation in alpha-1 antitrypsin deficiency. *Epigenetics.*, *7*, 720-728. doi: 710.4161/epi.20319. Epub 22012 Jul 20311. **02**

(76) Sin, D. D., Man, S. F., McWilliams, A., and Lam, S. (2006) Progression of airway dysplasia and C-reactive protein in smokers at high risk of lung cancer. *Am J Respir Crit Care Med.*, *173*, 535-539. Epub 2005 Dec 2009. **D, C**

(77) van Dijk, W. D., Akkermans, R., Heijdra, Y., Weel, C., Schermer, T. R., Scheepers, P. T., and Lenders, J. W. (2013) The acute effect of cigarette smoking on the high-sensitivity CRP and fibrinogen biomarkers in chronic obstructive pulmonary disease patients. *Biomark Med.*, *7*, 211-219. doi: 210.2217/bmm.2212.2112. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(78) van Doorn, M. B., Espirito Santo, S. M., Meijer, P., Kamerling, I. M., Schoemaker, R. C., Dirsch, V., Vollmar, A., Haffner, T., Gebhardt, R., Cohen, A. F., Princen, H. M., and Burggraaf, J. (2006) Effect of garlic powder on C-reactive protein and plasma lipids in overweight and smoking subjects. *Am J Clin Nutr.*, *84*, 1324-1329. **03**

(79) van Ree, R. M., de Vries, A. P., Oterdoom, L. H., The, T. H., Gansevoort, R. T., Homan van der Heide, J. J., van Son, W. J., Ploeg, R. J., de Jong, P. E., Gans, R. O., and Bakker, S. J. (2005) Abdominal obesity and smoking are important determinants of C-reactive protein in renal transplant recipients. *Nephrol Dial Transplant.*, *20*, 2524-2531. Epub 2005 Aug 2522. **03**

(80) Agrawal, A., Gang, T. B., and Rusinol, A. E. (2014) Recognition functions of pentameric C-reactive protein in cardiovascular disease. *Mediators Inflamm*, *2014:319215.*, 10.1155/2014/319215. Epub 312014 May 319219. **A**

(81) Anand, S. S., and Yusuf, S. (2010) C-reactive protein is a bystander of cardiovascular disease. *Eur Heart J.*, *31*, 2092-2096. doi: 2010.1093/eurheartj/ehq2242. Epub 2010 Jul 2030. **A**

(82) Bisoendial, R. J., Boekholdt, S. M., Vergeer, M., Stroes, E. S., and Kastelein, J. J. (2010) C-reactive protein is a mediator of cardiovascular disease. *Eur Heart J.*, *31*, 2087-2091. doi: 2010.1093/eurheartj/ehq2238. Epub 2010 Aug 2083. **A**

(83) Corsetti, J. P., Bakker, S. J., Sparks, C. E., and Dullaart, R. P. (2012) Apolipoprotein A-II influences apolipoprotein E-linked cardiovascular disease risk in women with high levels of HDL cholesterol and C-reactive protein. *PLoS One*, *7*, e39110. doi: 39110.31371/journal.pone.0039110. Epub 0032012 Jun 0039118. **04**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(84) Corsetti, J. P., Gansevoort, R. T., Bakker, S. J., Navis, G., Sparks, C. E., and Dullaart, R. P. (2012) Apolipoprotein E predicts incident cardiovascular disease risk in women but not in men with concurrently high levels of high-density lipoprotein cholesterol and C-reactive protein. *Metabolism.*, *61*, 996-1002. doi: 1010.1016/j.metabol.2011.1011.1010. Epub 2012 Jan 1005. **04**

(85) Corsetti, J. P., Gansevoort, R. T., Navis, G., Sparks, C. E., and Dullaart, R. P. (2011) LPL polymorphism (D9N) predicts cardiovascular disease risk directly and through interaction with CETP polymorphism (TaqIB) in women with high HDL cholesterol and CRP. *Atherosclerosis.*, *214*, 373-376. doi: 310.1016/j.atherosclerosis.2010.1011.1029. Epub 2010 Nov 1026. **04**

(86) De Luca, A., de Gaetano Donati, K., Colafigli, M., Cozzi-Lepri, A., De Curtis, A., Gori, A., Sighinolfi, L., Giacometti, A., Capobianchi, M. R., D'Avino, A., Iacoviello, L., Cauda, R., and D'Arminio Monforte, A. (2013) The association of high-sensitivity c-reactive protein and other biomarkers with cardiovascular disease in patients treated for HIV: a nested case-control study. *BMC Infect Dis.*, *13:414.*, 10.1186/1471-2334-1113-1414. **02**

(87) Hingorani, A. D., Sofat, R., Morris, R. W., Whincup, P., Lowe, G. D., Mindell, J., Sattar, N., Casas, J. P., and Shah, T. (2012) Is it important to measure or reduce C-reactive protein in people at risk of cardiovascular disease? *Eur Heart J.*, *33*, 2258-2264. doi: 2210.1093/eurheartj/ehs2168. Epub 2012 Jul 2255. **A**

(88) Jeppesen, J., and Asferg, C. (2010) C-reactive protein and cardiovascular disease: differences between humans and mice. *Hypertension.*, *56*, e15; author reply e16. doi: 10.1161/HYPERTENSIONAHA.1110.155077. Epub 152010 May 155017. **05**

(89) Kaptoge, S., Di Angelantonio, E., Pennells, L., Wood, A. M., White, I. R., Gao, P., Walker, M., Thompson, A., Sarwar, N., Caslake, M., Butterworth, A. S., Amouyel, P., Assmann, G., Bakker, S. J., Barr, E. L., Barrett-Connor, E., Benjamin, E. J., Bjorkelund, C., Brenner, H., Brunner, E., Clarke, R., Cooper, J.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

A., Cremer, P., Cushman, M., Dagenais, G. R., D'Agostino, R. B., Sr., Dankner, R., Davey-Smith, G., Deeg, D., Dekker, J. M., Engstrom, G., Folsom, A. R., Fowkes, F. G., Gallacher, J., Gaziano, J. M., Giampaoli, S., Gillum, R. F., Hofman, A., Howard, B. V., Ingelsson, E., Iso, H., Jorgensen, T., Kiechl, S., Kitamura, A., Kiyohara, Y., Koenig, W., Kromhout, D., Kuller, L. H., Lawlor, D. A., Meade, T. W., Nissinen, A., Nordestgaard, B. G., Onat, A., Panagiotakos, D. B., Psaty, B. M., Rodriguez, B., Rosengren, A., Salomaa, V., Kauhanen, J., Salonen, J. T., Shaffer, J. A., Shea, S., Ford, I., Stehouwer, C. D., Strandberg, T. E., Tipping, R. W., Tosetto, A., Wassertheil-Smoller, S., Wennberg, P., Westendorp, R. G., Whincup, P. H., Wilhelmsen, L., Woodward, M., Lowe, G. D., Wareham, N. J., Khaw, K. T., Sattar, N., Packard, C. J., Gudnason, V., Ridker, P. M., Pepys, M. B., Thompson, S. G., and Danesh, J. (2012) C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med.*, *367*, 1310-1320. doi: 1310.1056/NEJMoa1107477. **A**

(90) Kengne, A. P., Batty, G. D., Hamer, M., Stamatakis, E., and Czernichow, S. (2012) Association of C-reactive protein with cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants from four U.K. prospective cohort studies. *Diabetes Care.*, *35*, 396-403. doi: 310.2337/dc2311-1588. Epub 2011 Dec 2330. **A**

(91) Kones, R. (2010) Rosuvastatin, inflammation, C-reactive protein, JUPITER, and primary prevention of cardiovascular disease--a perspective. *Drug Des Devel Ther.*, *4:383-413.*, 10.2147/DDDT.S10812. **02**

(92) Koppolu, P., Durvasula, S., Palaparthy, R., Rao, M., Sagar, V., Reddy, S. K., and Lingam, S. (2013) Estimate of CRP and TNF-alpha level before and after periodontal therapy in cardiovascular disease patients. *Pan Afr Med J.*, *15:92.*, 10.11604/pamj.12013.11615.11692.12326. eCollection 12013. **02**

(93) Manace, L. C., and Babyatsky, M. W. (2012) Putting genome analysis to good use: lessons from C-reactive protein and cardiovascular disease. *Cleve Clin J Med.*, *79*, 182-191. doi: 110.3949/ccjm.3979a.09169. **A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(94) Noren Hooten, N., Ejiogu, N., Zonderman, A. B., and Evans, M. K. (2012) Association of oxidative DNA damage and C-reactive protein in women at risk for cardiovascular disease. *Arterioscler Thromb Vasc Biol.*, *32*, 2776-2784. doi: 2710.1161/ATVBAHA.2112.300276. Epub 302012 Sep 300213. **A**

(95) Out, D., Hall, R. J., Granger, D. A., Page, G. G., and Woods, S. J. (2012) Assessing salivary C-reactive protein: longitudinal associations with systemic inflammation and cardiovascular disease risk in women exposed to intimate partner violence. *Brain Behav Immun.*, *26*, 543-551. doi: 510.1016/j.bbi.2012.1001.1019. Epub 2012 Feb 1012. **A, D**

(96) Rahsepar, A. A., Mirzaee, A., Moodi, F., Moohebati, M., Tavallaie, S., Khorashadizadeh, F., Eshraghi, A., Alavi, M. S., Zarrabi, L., Sajjadian, M., Amini, M., Khojasteh, R., Paydar, R., Mousavi, S., Ghayour-Mobarhan, M., and Ferns, G. A. (2013) Changes in anti-heat shock protein 27 antibody and C-reactive protein levels following cardiac surgery and their association with cardiac function in patients with cardiovascular disease. *Cell Stress Chaperones.*, *18*, 65-74. doi: 10.1007/s12192-12012-10358-y. Epub 12012 Jul 12130. **02**

(97) Ridker, P. M. (2014) Inflammation, C-reactive protein, and cardiovascular disease: moving past the marker versus mediator debate. *Circ Res.*, *114*, 594-595. doi: 510.1161/CIRCRESAHA.1114.303215. **A**

(98) Seo, S. M., Baek, S. H., Jeon, H. K., Kang, S. M., Kim, D. S., Kim, W. S., Kim, H. S., Rha, S. W., Park, J. S., Seong, I. W., Ahn, Y. K., Yoon, J. H., and Cha, T. J. (2013) Correlations between the level of high-sensitivity C-reactive protein and cardiovascular risk factors in Korean adults with cardiovascular disease or diabetes mellitus: the CALLISTO study. *J Atheroscler Thromb*, *20*, 616-622. Epub 2013 May 2016. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(99) Sung, J. H., Lee, J. E., Samdarshi, T. E., Nagarajarao, H. S., Taylor, J. K., Agrawal, K. K., Taylor, H. A., Jr., and Fox, E. R. (2014) C-reactive protein and subclinical cardiovascular disease among African-Americans: (the Jackson Heart Study). *J Cardiovasc Med (Hagerstown). 15*, 371-376. doi: 310.2459/JCM.2450b2013e32836411d32836416. **A**

(100) Vepsalainen, T., Soinio, M., Marniemi, J., Lehto, S., Juutilainen, A., Laakso, M., and Ronnemaa, T. (2011) Physical activity, high-sensitivity C-reactive protein, and total and cardiovascular disease mortality in type 2 diabetes. *Diabetes Care.*, *34*, 1492-1496. doi: 1410.2337/dc1411-0469. Epub 2011 May 1420. **03**

(101) von Kanel, R., Mills, P. J., Mausbach, B. T., Dimsdale, J. E., Patterson, T. L., Ziegler, M. G., Ancoli-Israel, S., Allison, M., Chattillion, E. A., and Grant, I. (2012) Effect of Alzheimer caregiving on circulating levels of C-reactive protein and other biomarkers relevant to cardiovascular disease risk: a longitudinal study. *Gerontology*, *58*, 354-365. doi: 310.1159/000334219. Epub 000332011 Nov 000334229. **03**

(102) Wannamethee, S. G., Welsh, P., Lowe, G. D., Gudnason, V., Di Angelantonio, E., Lennon, L., Rumley, A., Whincup, P. H., and Sattar, N. (2011) N-terminal pro-brain natriuretic Peptide is a more useful predictor of cardiovascular disease risk than C-reactive protein in older men with and without pre-existing cardiovascular disease. *J Am Coll Cardiol.*, *58*, 56-64. doi: 10.1016/j.jacc.2011.1002.1041. **01**

(103) Young, D., Camhi, S., Wu, T., Hagberg, J., and Stefanick, M. (2013) Relationships among changes in C-reactive protein and cardiovascular disease risk factors with lifestyle interventions. *Nutr Metab Cardiovasc Dis.*, *23*, 857-863. doi: 810.1016/j.numecd.2012.1005.1003. Epub 2012 Jul 1024. **A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(104) Yousuf, O., Mohanty, B. D., Martin, S. S., Joshi, P. H., Blaha, M. J., Nasir, K., Blumenthal, R. S., and Budoff, M. J. (2013) High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? *J Am Coll Cardiol.*, *62*, 397-408. doi: 310.1016/j.jacc.2013.1005.1016. Epub 2013 May 1030. **A, R**

(105) Andreeva, E., and Melbye, H. (2014) Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. *BMC Fam Pract.*, *15:80.*, 10.1186/1471-2296-1115-1180. **B**

(106) Cals, J. W., Ament, A. J., Hood, K., Butler, C. C., Hopstaken, R. M., Wassink, G. F., and Dinant, G. J. (2011) C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. *J Eval Clin Pract.*, *17*, 1059-1069. doi: 1010.1111/j.1365-2753.2010.01472.x. Epub 02010 Jul 01478. **B**

(107) Cals, J. W., de Bock, L., Beckers, P. J., Francis, N. A., Hopstaken, R. M., Hood, K., de Bont, E. G., Butler, C. C., and Dinant, G. J. (2013) Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. *Ann Fam Med.*, *11*, 157-164. doi: 110.1370/afm.1477. **B**

(108) Engel, M. F., Paling, F. P., Hoepelman, A. I., van der Meer, V., and Oosterheert, J. J. (2012) Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review. *Fam Pract.*, *29*, 383-393. doi: 310.1093/fampra/cmr1119. Epub 2011 Dec 1098. **B**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(109) Fazli, M., O'Connell, A., Nilsson, M., Niehaus, K., Dow, J. M., Givskov, M., Ryan, R. P., and Tolker-Nielsen, T. (2011) The CRP/FNR family protein Bcam1349 is a c-di-GMP effector that regulates biofilm formation in the respiratory pathogen Burkholderia cenocepacia. *Mol Microbiol.*, *82*, 327-341. doi: 310.1111/j.1365-2958.2011.07814.x. Epub 02011 Sep 07817. **05**

(110) Gimeno, D., Delclos, G. L., Ferrie, J. E., De Vogli, R., Elovainio, M., Marmot, M. G., and Kivimaki, M. (2011) Association of CRP and IL-6 with lung function in a middle-aged population initially free from self-reported respiratory problems: the Whitehall II study. *Eur J Epidemiol.*, *26*, 135-144. doi: 110.1007/s10654-10010-19526-10655. Epub 12011 Feb 10654. **B**

(111) Huang, Y., Chen, R., Wu, T., Wei, X., and Guo, A. (2013) Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. *Br J Gen Pract.*, *63*, e787-794. doi: 710.3399/bjgp3313X674477. **B**

(112) Kavanagh, K. E., O'Shea, E., Halloran, R., Cantillon, P., and Murphy, A. W. (2011) A pilot study of the use of near-patient C-Reactive Protein testing in the treatment of adult respiratory tract infections in one Irish general practice. *BMC Fam Pract.*, *12:93.*, 10.1186/1471-2296-1112-1193. **B**

(113) Ling, M. R., Chapple, I. L., Creese, A. J., and Matthews, J. B. (2014) Effects of C-reactive protein on the neutrophil respiratory burst in vitro. *Innate Immun.*, *20*, 339-349. doi: 310.1177/1753425913493199. Epub 1753425913492013 Jul 1753425913493199. **05**

(114) Llor, C., Sierra, N., Hernandez, S., Moragas, A., Hernandez, M., Bayona, C., and Miravitlles, M. (2010) Impact of C-reactive protein testing on adherence to thrice-daily antibiotic regimens in patients with lower respiratory tract infection. *Prim Care Respir J.*, *19*, 358-362. doi: 310.4104/pcrj.2010.00023. **B**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(115) Mezzomo, A., Bodin, O. L., Jr., and Lucia, V. (2011) Preoperative C-reactive protein predicts respiratory infection after coronary artery bypass graft surgery. *Arq Bras Cardiol.*, *97*, 365-371. Epub 2011 Sep 2030. **02**

(116) Morales, E., Guerra, S., Garcia-Esteban, R., Guxens, M., Alvarez-Pedrerol, M., Bustamante, M., Estivill, X., Anto, J. M., and Sunyer, J. (2011) Maternal C-reactive protein levels in pregnancy are associated with wheezing and lower respiratory tract infections in the offspring. *Am J Obstet Gynecol.*, *204*, 164.e161-169. doi: 110.1016/j.ajog.2010.1008.1056. Epub 2010 Oct 1025. **03**

(117) Naidoo, T., Konkol, K., Biccard, B., Dudose, K., and McKune, A. J. (2012) Elevated salivary C-reactive protein predicted by low cardio-respiratory fitness and being overweight in African children. *Cardiovasc J Afr.*, *23*, 501-506. doi: 510.5830/CVJA-2012-5058. **03**

(118) Ozsu, S., Yilmaz, G., Yilmaz, I., Oztuna, F., Bulbul, Y., and Ozlu, T. (2011) C-reactive protein alone or combined with cardiac troponin T for risk stratification of respiratory intensive care unit patients. *Respir Care.*, *56*, 1002-1008. doi: 1010.4187/respcare.01007. Epub 02011 Feb 01021. **03**

(119) Rego, M. A., Martinez, F. E., Elias, J., and Mussi-Pinhata, M. M. (2010) Diagnostic value of interleukin-6 and C-reactive protein on early onset bacterial infection in preterm neonates with respiratory distress. *J Perinat Med.*, *38*, 527-533. doi: 510.1515/JPM.2010.1071. **02**

(120) Sonnenschein-van der Voort, A. M., Jaddoe, V. W., Moll, H. A., Hofman, A., van der Valk, R. J., de Jongste, J. C., and Duijts, L. (2013) Influence of maternal and cord blood C-reactive protein on childhood respiratory symptoms and eczema. *Pediatr Allergy Immunol.*, *24*, 469-475. doi: 410.1111/pai.12094. Epub 12013 Jun 12016. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(121) Xu, P. C., Hao, J., Yang, X. W., Chang, D. Y., Chen, M., and Zhao, M. H. (2012) C-reactive protein enhances the respiratory burst of neutrophils-induced by antineutrophil cytoplasmic antibody. *Mol Immunol.*, *52*, 148-154. doi: 110.1016/j.molimm.2012.1005.1012. Epub 2012 Jun 1017. **05**

(122) Alifano, M., Falcoz, P. E., Seegers, V., Roche, N., Schussler, O., Younes, M., Antonacci, F., Forgez, P., Dechartres, A., Massard, G., Damotte, D., and Regnard, J. F. (2011) Preresection serum C-reactive protein measurement and survival among patients with resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg.*, *142*, 1161-1167. doi: 1110.1016/j.jtcvs.2011.1107.1021. Epub 2011 Aug 1126. **C**

(123) Allin, K. H., Bojesen, S. E., Johansen, J. S., and Nordestgaard, B. G. (2012) Cancer risk by combined levels of YKL-40 and C-reactive protein in the general population. *Br J Cancer.*, *106*, 199-205. doi: 110.1038/bjc.2011.1501. Epub 2011 Nov 1017. **C**

(124) Allin, K. H., and Nordestgaard, B. G. (2011) Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci.*, *48*, 155-170. doi: 110.3109/10408363.10402011.10599831. **C, R**

(125) Douglas, J. B., Silverman, D. T., Weinstein, S. J., Graubard, B. I., Pollak, M. N., Tao, Y., Virtamo, J., Albanes, D., and Stolzenberg-Solomon, R. Z. (2011) Serum C-reactive protein and risk of pancreatic cancer in two nested, case-control studies. *Cancer Epidemiol Biomarkers Prev.*, *20*, 359-369. doi: 310.1158/1055-9965.EPI-1110-1024. Epub 2010 Dec 1120. **C**

(126) Guo, Y. Z., Pan, L., Du, C. J., Ren, D. Q., and Xie, X. M. (2013) Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. *Asian Pac J Cancer Prev*, *14*, 243-248. **C**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(127) Heikkila, K., Silander, K., Salomaa, V., Jousilahti, P., Koskinen, S., Pukkala, E., and Perola, M. (2011) C-reactive protein-associated genetic variants and cancer risk: findings from FINRISK 1992, FINRISK 1997 and Health 2000 studies. *Eur J Cancer.*, *47*, 404-412. doi: 410.1016/j.ejca.2010.1007.1032. Epub 2010 Aug 1018. **C**

(128) Hong, S., Kang, Y. A., Cho, B. C., and Kim, D. J. (2012) Elevated serum C-reactive protein as a prognostic marker in small cell lung cancer. *Yonsei Med J.*, *53*, 111-117. doi: 110.3349/ymj.2012.3353.3341.3111. **C**

(129) Kanoh, Y., Abe, T., Masuda, N., and Akahoshi, T. (2013) Progression of non-small cell lung cancer: diagnostic and prognostic utility of matrix metalloproteinase-2, C-reactive protein and serum amyloid A. *Oncol Rep.*, *29*, 469-473. doi: 410.3892/or.2012.2123. Epub 2012 Nov 3895. **C**

(130) Ko, Y. J., Kwon, Y. M., Kim, K. H., Choi, H. C., Chun, S. H., Yoon, H. J., Goh, E., Cho, B., and Park, M. (2012) High-sensitivity C-reactive protein levels and cancer mortality. *Cancer Epidemiol Biomarkers Prev.*, *21*, 2076-2086. doi: 2010.1158/1055-9965.EPI-2012-0611. **C**

(131) Kruse, A. L., Luebbers, H. T., and Gratz, K. W. (2010) C-reactive protein levels: a prognostic marker for patients with head and neck cancer? *Head Neck Oncol.*, *2:21.*, 10.1186/1758-3284-1182-1121. **C**

(132) Lukaszewicz-Zajac, M., Mroczko, B., and Szmitkowski, M. (2010) [The role of interleukin-6 and C-reactive protein in gastric cancer]. *Pol Merkur Lekarski.*, *29*, 382-386. **C**

(133) Masago, K., Fujita, S., Togashi, Y., Kim, Y. H., Hatachi, Y., Fukuhara, A., Nagai, H., Irisa, K., Sakamori, Y., Okuda, C., Mio, T., and Mishima, M. (2010) Clinical significance of pretreatment C-reactive protein in patients with advanced nonsquamous, non-small cell lung cancer who received gefitinib. *Oncology*, *79*, 355-362. doi: 310.1159/000323486. Epub 000322011 Mar 000323424. **02**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(134) Matsumoto, T., Fujita, M., Hirota, T., Takeda, S., Hirano, R., Uchino, J., Harada, T., and Watanabe, K. (2013) Elevation of serum C-reactive protein predicts failure of the initial antimicrobial treatment for febrile neutropenia with lung cancer. *J Infect Chemother.*, *19*, 202-207. doi: 210.1007/s10156-10012-10474-10158. Epub 12012 Sep 10128. **02**

(135) Minamiya, Y., Miura, M., Hinai, Y., Saito, H., Ito, M., Imai, K., Ono, T., Motoyama, S., and Ogawa, J. (2010) The CRP 1846T/T genotype is associated with a poor prognosis in patients with non-small cell lung cancer. *Tumour Biol.*, *31*, 673-679. doi: 610.1007/s13277-13010-10086-13279. Epub 12010 Aug 13275. **02**

(136) O'Dowd, C., McRae, L. A., McMillan, D. C., Kirk, A., and Milroy, R. (2010) Elevated preoperative C-reactive protein predicts poor cancer specific survival in patients undergoing resection for non-small cell lung cancer. *J Thorac Oncol.*, *5*, 988-992. doi: 910.1097/JTO.1090b1013e3181da1078f1099. **02**

(137) Park, D. S., Kim, D., Hwang, K. E., Hwang, Y. R., Park, C., Seol, C. H., Cho, K. H., Kim, B. R., Park, S. H., Jeong, E. T., and Kim, H. R. (2013) Diagnostic value and prognostic significance of pleural C-reactive protein in lung cancer patients with malignant pleural effusions. *Yonsei Med J.*, *54*, 396-402. doi: 310.3349/ymj.2013.3354.3342.3396. **02**

(138) Pine, S. R., Mechanic, L. E., Enewold, L., Chaturvedi, A. K., Katki, H. A., Zheng, Y. L., Bowman, E. D., Engels, E. A., Caporaso, N. E., and Harris, C. C. (2011) Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. *J Natl Cancer Inst.*, *103*, 1112-1122. doi: 1110.1093/jnci/djr1216. Epub 2011 Jun 1117. **C**

(139) Shen, L., Li, Z. M., and Lu, S. (2011) [Clinical significance of C-reactive protein in patients with stage I non-small cell lung cancer]. *Zhonghua Zhong Liu Za Zhi.*, *33*, 442-446. **02**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(140) Srimuninnimit, V., Ariyapanya, S., Nimmannit, A., Wonglaksanapimon, S., Akewanlop, C., and Soparattanapaisarn, N. (2012) C-reactive protein as a monitor of chemotherapy response in advanced non-small cell lung cancer (CML study). *J Med Assoc Thai.*, *95*, S199-207. **02**

(141) Szkandera, J., Stotz, M., Absenger, G., Stojakovic, T., Samonigg, H., Kornprat, P., Schaberl-Moser, R., Alzoughbi, W., Lackner, C., Ress, A. L., Seggewies, F. S., Gerger, A., Hoefler, G., and Pichler, M. (2014) Validation of C-reactive protein levels as a prognostic indicator for survival in a large cohort of pancreatic cancer patients. *Br J Cancer.*, *110*, 183-188. doi: 110.1038/bjc.2013.1701. Epub 2013 Nov 1037. **02**

(142) Terata, K., Motoyama, S., Kamata, S., Hinai, Y., Miura, M., Sato, Y., Yoshino, K., Ito, A., Imai, K., Saito, H., and Minamiya, Y. (2014) Evaluation of the potential for lymph node metastasis using CRP 1846C>T genetic polymorphism in invasive breast cancer. *Tumour Biol.*, *35*, 5931-5935. doi: 5910.1007/s13277-13014-11786-13273. Epub 12014 Mar 13216. **02**

(143) Tomita, M., Shimizu, T., Ayabe, T., Nakamura, K., and Onitsuka, T. (2012) Elevated preoperative inflammatory markers based on neutrophil-to-lymphocyte ratio and C-reactive protein predict poor survival in resected non-small cell lung cancer. *Anticancer Res.*, *32*, 3535-3538. **02**

(144) Vaguliene, N., Zemaitis, M., Miliauskas, S., Urboniene, D., Sitkauskiene, B., and Sakalauskas, R. (2011) Comparison of C-reactive protein levels in patients with lung cancer and chronic obstructive pulmonary disease. *Medicina (Kaunas)*, *47*, 421-427. Epub 2011 Nov 2018. **C, B**

(145) Xu, M., Zhu, M., Du, Y., Yan, B., Wang, Q., Wang, C., and Zhao, J. (2013) Serum C-reactive protein and risk of lung cancer: a case-control study. *Med Oncol.*, *30*, 319. doi: 310.1007/s12032-12012-10319-12034. Epub 12012 Dec 12015. **02**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(146) Xu, Y., Li, Z., and Shen-Tu, Y. (2011) [The prognostic value of detection of serum C-reactive protein in the patients with stage I lung cancer]. *Zhongguo Fei Ai Za Zhi.*, *14*, 400-403. doi: 410.3779/j.issn.1009-3419.2011.3705.3704. **02**

(147) Zhou, B., Liu, J., Wang, Z. M., and Xi, T. (2012) C-reactive protein, interleukin 6 and lung cancer risk: a meta-analysis. *PLoS One*, *7*, e43075. doi: 43010.41371/journal.pone.0043075. Epub 0042012 Aug 0043017. **C**

(148) Bazzano, L. A., He, J., Muntner, P., Vupputuri, S., and Whelton, P. K. (2003) Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med.*, *138*, 891-897. **D, E, F**

(149) Bermudez, E. A., Rifai, N., Buring, J., Manson, J. E., and Ridker, P. M. (2002) Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. *Arterioscler Thromb Vasc Biol.*, *22*, 1668-1673. **D, F**

(150) Calapai, G., Caputi, A. P., Mannucci, C., Gregg, E. O., Pieratti, A., Aurora, R. G., Chaudhary, N., Puntoni, R., Lowe, F., McEwan, M., Bassi, A., Morandi, S., and Nunziata, A. (2009) A cross-sectional investigation of biomarkers of risk after a decade of smoking. *Inhal.Toxicol.*, *21*, 1138-1143. **D**

(151) Crook, M. A., Scott, D. A., Stapleton, J. A., Palmer, R. M., Wilson, R. F., and Sutherland, G. (2000) Circulating concentrations of C-reactive protein and total sialic acid in tobacco smokers remain unchanged following one year of validated smoking cessation. *Eur J Clin Invest.*, *30*, 861-865. **D, E, F**

(152) Fredrikson, G. N., Hedblad, B., Nilsson, J. A., Alm, R., Berglund, G., and Nilsson, J. (2004) Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma C-reactive protein levels. *Metabolism.*, *53*, 1436-1442. **D**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(153) Frohlich, M., Sund, M., Lowel, H., Imhof, A., Hoffmeister, A., and Koenig, W. (2003) Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). *Eur Heart J.*, *24*, 1365-1372. **D, E, F**

(154) Frost-Pineda, K., Liang, Q., Liu, J., Rimmer, L., Jin, Y., Feng, S., Kapur, S., Mendes, P., Roethig, H., and Sarkar, M. (2011) Biomarkers of Potential Harm Among Adult Smokers and Nonsmokers in the Total Exposure Study. *Nicotine.Tob.Res.*, *13*, 182-193. **D**

(155) Garcia-Lorda, P., Bullo, M., Balanza, R., and Salas-Salvado, J. (2006) C-reactive protein, adiposity and cardiovascular risk factors in a Mediterranean population. *Int J Obes (Lond). 30*, 468-474. **D, A**

(156) Helmersson, J., Larsson, A., Vessby, B., and Basu, S. (2005) Active smoking and a history of smoking are associated with enhanced prostaglandin F(2alpha), interleukin-6 and F2-isoprostane formation in elderly men. *Atherosclerosis.*, *181*, 201-207. Epub 2005 Apr 2026. **D, F, A**

(157) Kiechl, S., Werner, P., Egger, G., Oberhollenzer, F., Mayr, M., Xu, Q., Poewe, W., and Willeit, J. (2002) Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. *Stroke.*, *33*, 2170-2176. **D, E, F**

(158) Koenig, W., Sund, M., Frohlich, M., Fischer, H. G., Lowel, H., Doring, A., Hutchinson, W. L., and Pepys, M. B. (1999) C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation.*, *99*, 237-242. **D, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(159) Kuller, L. H., Tracy, R. P., Shaten, J., and Meilahn, E. N. (1996) Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J Epidemiol.*, *144*, 537-547. **A**

(160) Lavi, S., Prasad, A., Yang, E. H., Mathew, V., Simari, R. D., Rihal, C. S., Lerman, L. O., and Lerman, A. (2007) Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. *Circulation.*, *115*, 2621-2627. Epub 2007 May 2627. **D, A**

(161) Levitzky, Y. S., Guo, C. Y., Rong, J., Larson, M. G., Walter, R. E., Keaney, J. F., Jr., Sutherland, P. A., Vasan, A., Lipinska, I., Evans, J. C., and Benjamin, E. J. (2008) Relation of smoking status to a panel of inflammatory markers: the framingham offspring. *Atherosclerosis.*, *201*, 217-224. doi: 210.1016/j.atherosclerosis.2007.1012.1058. Epub 2008 Mar 1014. **D, F**

(162) Lowe, G. D., Yarnell, J. W., Rumley, A., Bainton, D., and Sweetnam, P. M. (2001) C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis? *Arterioscler Thromb Vasc Biol.*, *21*, 603-610. **D, E, F, A**

(163) Mendall, M. A., Patel, P., Ballam, L., Strachan, D., and Northfield, T. C. (1996) C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *BMJ.*, *312*, 1061-1065. **D, A**

(164) Panagiotakos, D. B., Pitsavos, C., Chrysohoou, C., Skoumas, J., Masoura, C., Toutouzas, P., and Stefanadis, C. (2004) Effect of exposure to secondhand smoke on markers of inflammation: the ATTICA study. *Am J Med.*, *116*, 145-150. **D, F**

(165) Pirkola, J., Vaarasmaki, M., Ala-Korpela, M., Bloigu, A., Canoy, D., Hartikainen, A. L., Leinonen, M., Miettola, S., Paldanius, M., Tammelin, T. H., Jarvelin, M. R., and Pouta, A. (2010) Low-grade, systemic inflammation in adolescents: association with early-life factors, gender, and lifestyle. *Am J Epidemiol.*, *171*, 72-82. doi: 10.1093/aje/kwp1320. Epub 2009 Nov 1016. **D**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(166) Roethig, H. J., Feng, S., Liang, Q., Liu, J., Rees, W. A., and Zedler, B. K. (2008) A 12-Month, Randomized, Controlled Study to Evaluate Exposure and Cardiovascular Risk Factors in Adult Smokers Switching From Conventional Cigarettes to a Second-Generation Electrically Heated Cigarette Smoking System. *J.Clin.Pharmacol.*, *48*, 580-591. **D, G**

(167) Rohde, L. E., Hennekens, C. H., and Ridker, P. M. (1999) Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol.*, *84*, 1018-1022. **D, E, F, A**

(168) Yamada, S., Gotoh, T., Nakashima, Y., Kayaba, K., Ishikawa, S., Nago, N., Nakamura, Y., Itoh, Y., and Kajii, E. (2001) Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population : Jichi Medical School Cohort Study. *Am J Epidemiol.*, *153*, 1183-1190. **D**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.2 Appendix 2 Inclusion criteria A

(1) Life Sciences Research Office (LSRO). (2007) *Biological effects assessment in the evaluation of potential reduced-risk tobacco products*. Bethesda, Maryland, USA. **R, A, D, E, F**

(2) US Department of Health and Human Services. (2010) *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*

A Report of the Surgeon General. **R, A, D, F**

(6) Blaschke, F., Bruemmer, D., Yin, F., Takata, Y., Wang, W., Fishbein, M. C., Okura, T., Higaki, J., Graf, K., Fleck, E., Hsueh, W. A., and Law, R. E. (2004) C-reactive protein induces apoptosis in human coronary vascular smooth muscle cells. *Circulation.*, *110*, 579-587. Epub 2004 Jul 2026. **A**

(7) Burke, A. P., Tracy, R. P., Kolodgie, F., Malcom, G. T., Zieske, A., Kutys, R., Pestaner, J., Smialek, J., and Virmani, R. (2002) Elevated C-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies. *Circulation.*, *105*, 2019-2023. **A**

(9) Danesh, J., Wheeler, J. G., Hirschfield, G. M., Eda, S., Eiriksdottir, G., Rumley, A., Lowe, G. D., Pepys, M. B., and Gudnason, V. (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med.*, *350*, 1387-1397. **A**

(10) Fu, T., and Borensztajn, J. (2002) Macrophage uptake of low-density lipoprotein bound to aggregated C-reactive protein: possible mechanism of foam-cell formation in atherosclerotic lesions. *Biochem J.*, *366*, 195-201. **A**

(14) Libby, P., Ridker, P. M., and Maseri, A. (2002) Inflammation and atherosclerosis. *Circulation.*, *105*, 1135-1143. **A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(16) Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., 3rd, Criqui, M., Fadl, Y. Y., Fortmann, S. P., Hong, Y., Myers, G. L., Rifai, N., Smith, S. C., Jr., Taubert, K., Tracy, R. P., and Vinicor, F. (2003) Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.*, *107*, 499-511. **A**

(17) Rackley, C. E. (2004) New clinical markers predictive of cardiovascular disease: the role of inflammatory mediators. *Cardiol Rev.*, *12*, 151-157. **A**

(18) Ridker, P. M., Brown, N. J., Vaughan, D. E., Harrison, D. G., and Mehta, J. L. (2004) Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation.*, *109*, IV6-19. **A**

(19) Tracy, R. P., and Kuller, L. H. (2005) C-reactive protein, heart disease risk, and the popular media. *Arch Intern Med.*, *165*, 2058-2060. **A**

(22) Verma, S., and Yeh, E. T. (2003) C-reactive protein and atherothrombosis--beyond a biomarker: an actual partaker of lesion formation. *Am J Physiol Regul Integr Comp Physiol.*, *285*, R1253-1256; discussion R1257-1258. **A**

(23) Vigushin, D. M., Pepys, M. B., and Hawkins, P. N. (1993) Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. *J Clin Invest.*, *91*, 1351-1357. **A**

(25) Corrado, E., and Novo, S. (2007) [High sensitivity of C-reactive protein in primary prevention]. *G Ital Cardiol (Rome). 8*, 327-334. **R, A**

(26) Fabijanic, D., Banic, M., and Kardum, D. (2006) [C-reactive protein in cardiovascular risk evaluation]. *Lijec Vjesn.*, *128*, 167-174. **R, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(27) Hemingway, H., Philipson, P., Chen, R., Fitzpatrick, N. K., Damant, J., Shipley, M., Abrams, K. R., Moreno, S., McAllister, K. S., Palmer, S., Kaski, J. C., Timmis, A. D., and Hingorani, A. D. (2010) Evaluating the quality of research into a single prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. *PLoS Med.*, *7*, e1000286. doi: 1000210.1001371/journal.pmed.1000286. **R, A**

(28) Kao, P. C., Shiesh, S. C., and Wu, T. J. (2006) Serum C-reactive protein as a marker for wellness assessment. *Ann Clin Lab Sci.*, *36*, 163-169. **R, A**

(32) Ridker, P. M. (2007) C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol.*, *49*, 2129-2138. Epub 2007 Apr 2130. **R, A**

(33) Ridker, P. M., and Silvertown, J. D. (2008) Inflammation, C-reactive protein, and atherothrombosis. *J Periodontol.*, *79*, 1544-1551. doi: 1510.1902/jop.2008.080249. **R, A**

(34) Rodrigues, I. M., and Klein, L. C. (2006) Boiled or filtered coffee? Effects of coffee and caffeine on cholesterol, fibrinogen and C-reactive protein. *Toxicol Rev*, *25*, 55-69. **R, A**

(35) Rudolf, J., and Lewandrowski, K. B. (2014) Cholesterol, lipoproteins, high-sensitivity c-reactive protein, and other risk factors for atherosclerosis. *Clin Lab Med*, *2014 Mar;34*, 113-127. **R, A**

(37) Tonstad, S., and Cowan, J. L. (2009) C-reactive protein as a predictor of disease in smokers and former smokers: a review. *Int J Clin Pract.*, *63*, 1634-1641. doi: 1610.1111/j.1742-1241.2009.02179.x. Epub 02009 Aug 02129. **R, A, C, D, E, F**

(38) Yosef-Levi, I. M., Grad, E., and Danenberg, H. D. (2007) [C-reactive protein and atherothrombosis--a prognostic factor or a risk factor?]. *Harefuah*, *2007 Dec;146*, 970-974. **R, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(39) Ahonen, T. M., Kautiainen, H. J., Keinanen-Kiukaanniemi, S. M., Kumpusalo, E. A., and Vanhala, M. J. (2008) Gender difference among smoking, adiponectin, and high-sensitivity C-reactive protein. *Am J Prev Med.*, *35*, 598-601. doi: 510.1016/j.amepre.2008.1009.1011. Epub 2008 Oct 1018. **D, E, F, A**

(69) O'Callaghan, P. A., Fitzgerald, A., Fogarty, J., Gaffney, P., Hanbidge, M., Boran, G., Enright, H., Murphy, J., McCarthy, B., and Graham, I. M. (2005) New and old cardiovascular risk factors: C-reactive protein, homocysteine, cysteine and von Willebrand factor increase risk, especially in smokers. *Eur J Cardiovasc Prev Rehabil.*, *12*, 542-547. **D, A**

(80) Agrawal, A., Gang, T. B., and Rusinol, A. E. (2014) Recognition functions of pentameric C-reactive protein in cardiovascular disease. *Mediators Inflamm*, *2014:319215.*, 10.1155/2014/319215. Epub 312014 May 319219. **A**

(81) Anand, S. S., and Yusuf, S. (2010) C-reactive protein is a bystander of cardiovascular disease. *Eur Heart J.*, *31*, 2092-2096. doi: 2010.1093/eurheartj/ehq2242. Epub 2010 Jul 2030. **A**

(82) Bisoendial, R. J., Boekholdt, S. M., Vergeer, M., Stroes, E. S., and Kastelein, J. J. (2010) C-reactive protein is a mediator of cardiovascular disease. *Eur Heart J.*, *31*, 2087-2091. doi: 2010.1093/eurheartj/ehq2238. Epub 2010 Aug 2083. **A**

(89) Kaptoge, S., Di Angelantonio, E., Pennells, L., Wood, A. M., White, I. R., Gao, P., Walker, M., Thompson, A., Sarwar, N., Caslake, M., Butterworth, A. S., Amouyel, P., Assmann, G., Bakker, S. J., Barr, E. L., Barrett-Connor, E., Benjamin, E. J., Bjorkelund, C., Brenner, H., Brunner, E., Clarke, R., Cooper, J. A., Cremer, P., Cushman, M., Dagenais, G. R., D'Agostino, R. B., Sr., Dankner, R., Davey-Smith, G., Deeg, D., Dekker, J. M., Engstrom, G., Folsom, A. R., Fowkes, F. G., Gallacher, J., Gaziano, J. M., Giampaoli, S., Gillum, R. F., Hofman, A., Howard, B. V., Ingelsson, E., Iso, H., Jorgensen, T., Kiechl, S., Kitamura, A., Kiyohara, Y., Koenig, W., Kromhout, D., Kuller, L. H., Lawlor, D. A., Meade, T. W., Nissinen, A., Nordestgaard, B. G., Onat, A., Panagiotakos, D.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

B., Psaty, B. M., Rodriguez, B., Rosengren, A., Salomaa, V., Kauhanen, J., Salonen, J. T., Shaffer, J. A., Shea, S., Ford, I., Stehouwer, C. D., Strandberg, T. E., Tipping, R. W., Tosetto, A., Wassertheil-Smoller, S., Wennberg, P., Westendorp, R. G., Whincup, P. H., Wilhelmsen, L., Woodward, M., Lowe, G. D., Wareham, N. J., Khaw, K. T., Sattar, N., Packard, C. J., Gudnason, V., Ridker, P. M., Pepys, M. B., Thompson, S. G., and Danesh, J. (2012) C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med.*, *367*, 1310-1320. doi: 1310.1056/NEJMoa1107477. **A**

(90) Kengne, A. P., Batty, G. D., Hamer, M., Stamatakis, E., and Czernichow, S. (2012) Association of C-reactive protein with cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants from four U.K. prospective cohort studies. *Diabetes Care.*, *35*, 396-403. doi: 310.2337/dc2311-1588. Epub 2011 Dec 2330. **A**

(93) Manace, L. C., and Babyatsky, M. W. (2012) Putting genome analysis to good use: lessons from C-reactive protein and cardiovascular disease. *Cleve Clin J Med.*, *79*, 182-191. doi: 110.3949/ccjm.3979a.09169. **A**

(94) Noren Hooten, N., Ejiogu, N., Zonderman, A. B., and Evans, M. K. (2012) Association of oxidative DNA damage and C-reactive protein in women at risk for cardiovascular disease. *Arterioscler Thromb Vasc Biol.*, *32*, 2776-2784. doi: 2710.1161/ATVBAHA.2112.300276. Epub 302012 Sep 300213. **A**

(95) Out, D., Hall, R. J., Granger, D. A., Page, G. G., and Woods, S. J. (2012) Assessing salivary C-reactive protein: longitudinal associations with systemic inflammation and cardiovascular disease risk in women exposed to intimate partner violence. *Brain Behav Immun.*, *26*, 543-551. doi: 510.1016/j.bbi.2012.1001.1019. Epub 2012 Feb 1012. **A, D**

(97) Ridker, P. M. (2014) Inflammation, C-reactive protein, and cardiovascular disease: moving past the marker versus mediator debate. *Circ Res.*, *114*, 594-595. doi: 510.1161/CIRCRESAHA.1114.303215. **A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(99) Sung, J. H., Lee, J. E., Samdarshi, T. E., Nagarajarao, H. S., Taylor, J. K., Agrawal, K. K., Taylor, H. A., Jr., and Fox, E. R. (2014) C-reactive protein and subclinical cardiovascular disease among African-Americans: (the Jackson Heart Study). *J Cardiovasc Med (Hagerstown). 15*, 371-376. doi: 310.2459/JCM.2450b2013e32836411d32836416. **A**

(103) Young, D., Camhi, S., Wu, T., Hagberg, J., and Stefanick, M. (2013) Relationships among changes in C-reactive protein and cardiovascular disease risk factors with lifestyle interventions. *Nutr Metab Cardiovasc Dis.*, *23*, 857-863. doi: 810.1016/j.numecd.2012.1005.1003. Epub 2012 Jul 1024. **A**

(104) Yousuf, O., Mohanty, B. D., Martin, S. S., Joshi, P. H., Blaha, M. J., Nasir, K., Blumenthal, R. S., and Budoff, M. J. (2013) High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? *J Am Coll Cardiol.*, *62*, 397-408. doi: 310.1016/j.jacc.2013.1005.1016. Epub 2013 May 1030. **A, R**

(155) Garcia-Lorda, P., Bullo, M., Balanza, R., and Salas-Salvado, J. (2006) C-reactive protein, adiposity and cardiovascular risk factors in a Mediterranean population. *Int J Obes (Lond). 30*, 468-474. **D, A**

(156) Helmersson, J., Larsson, A., Vessby, B., and Basu, S. (2005) Active smoking and a history of smoking are associated with enhanced prostaglandin F(2alpha), interleukin-6 and F2-isoprostane formation in elderly men. *Atherosclerosis.*, *181*, 201-207. Epub 2005 Apr 2026. **D, F, A**

(158) Koenig, W., Sund, M., Frohlich, M., Fischer, H. G., Lowel, H., Doring, A., Hutchinson, W. L., and Pepys, M. B. (1999) C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation.*, *99*, 237-242. **D, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(159) Kuller, L. H., Tracy, R. P., Shaten, J., and Meilahn, E. N. (1996) Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J Epidemiol.*, *144*, 537-547. **A**

(160) Lavi, S., Prasad, A., Yang, E. H., Mathew, V., Simari, R. D., Rihal, C. S., Lerman, L. O., and Lerman, A. (2007) Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. *Circulation.*, *115*, 2621-2627. Epub 2007 May 2627. **D, A**

(167) Rohde, L. E., Hennekens, C. H., and Ridker, P. M. (1999) Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol.*, *84*, 1018-1022. **D, E, F, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.3 Appendix 3 Inclusion criteria B

(40) Aksu, F., Capan, N., Aksu, K., Ofluoglu, R., Canbakan, S., Yavuz, B., and Akin, K. O. (2013) C-reactive protein levels are raised in stable Chronic obstructive pulmonary disease patients independent of smoking behavior and biomass exposure. *J Thorac Dis.*, *5*, 414-421. doi: 410.3978/j.issn.2072-1439.2013.3906.3927. **D, B**

(66) Melbye, H., Halvorsen, D. S., Hartz, I., Medbo, A., Brox, J., Eggen, A. E., and Njolstad, I. (2007) Bronchial airflow limitation, smoking, body mass index, and statin use are strongly associated with the C-reactive protein level in the elderly. The Tromso Study 2001. *Respir Med.*, *101*, 2541-2549. Epub 2007 Sep 2546. **D, B**

(72) Pinto-Plata, V. M., Mullerova, H., Toso, J. F., Feudjo-Tepie, M., Soriano, J. B., Vessey, R. S., and Celli, B. R. (2006) C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax.*, *61*, 23-28. Epub 2005 Sep 2002. **D, B**

(105) Andreeva, E., and Melbye, H. (2014) Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. *BMC Fam Pract.*, *15:80.*, 10.1186/1471-2296-1115-1180. **B**

(106) Cals, J. W., Ament, A. J., Hood, K., Butler, C. C., Hopstaken, R. M., Wassink, G. F., and Dinant, G. J. (2011) C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. *J Eval Clin Pract.*, *17*, 1059-1069. doi: 1010.1111/j.1365-2753.2010.01472.x. Epub 02010 Jul 01478. **B**

(107) Cals, J. W., de Bock, L., Beckers, P. J., Francis, N. A., Hopstaken, R. M., Hood, K., de Bont, E. G., Butler, C. C., and Dinant, G. J. (2013) Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. *Ann Fam Med.*, *11*, 157-164. doi: 110.1370/afm.1477. **B**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(108) Engel, M. F., Paling, F. P., Hoepelman, A. I., van der Meer, V., and Oosterheert, J. J. (2012) Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review. *Fam Pract.*, *29*, 383-393. doi: 310.1093/fampra/cmr1119. Epub 2011 Dec 1098. **B**

(110) Gimeno, D., Delclos, G. L., Ferrie, J. E., De Vogli, R., Elovainio, M., Marmot, M. G., and Kivimaki, M. (2011) Association of CRP and IL-6 with lung function in a middle-aged population initially free from self-reported respiratory problems: the Whitehall II study. *Eur J Epidemiol.*, *26*, 135-144. doi: 110.1007/s10654-10010-19526-10655. Epub 12011 Feb 10654. **B**

(111) Huang, Y., Chen, R., Wu, T., Wei, X., and Guo, A. (2013) Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. *Br J Gen Pract.*, *63*, e787-794. doi: 710.3399/bjgp3313X674477. **B**

(112) Kavanagh, K. E., O'Shea, E., Halloran, R., Cantillon, P., and Murphy, A. W. (2011) A pilot study of the use of near-patient C-Reactive Protein testing in the treatment of adult respiratory tract infections in one Irish general practice. *BMC Fam Pract.*, *12:93.*, 10.1186/1471-2296-1112-1193. **B**

(114) Llor, C., Sierra, N., Hernandez, S., Moragas, A., Hernandez, M., Bayona, C., and Miravitlles, M. (2010) Impact of C-reactive protein testing on adherence to thrice-daily antibiotic regimens in patients with lower respiratory tract infection. *Prim Care Respir J.*, *19*, 358-362. doi: 310.4104/pcrj.2010.00023. **B**

(144) Vaguliene, N., Zemaitis, M., Miliauskas, S., Urboniene, D., Sitkauskiene, B., and Sakalauskas, R. (2011) Comparison of C-reactive protein levels in patients with lung cancer and chronic obstructive pulmonary disease. *Medicina (Kaunas)*, *47*, 421-427. Epub 2011 Nov 2018. **C, B**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(162) Lowe, G. D., Yarnell, J. W., Rumley, A., Bainton, D., and Sweetnam, P. M. (2001) C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis? *Arterioscler Thromb Vasc Biol.*, *21*, 603-610. **D, E, F, A**

(163) Mendall, M. A., Patel, P., Ballam, L., Strachan, D., and Northfield, T. C. (1996) C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *BMJ.*, *312*, 1061-1065. **D, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.4 Appendix 4 Inclusion criteria C

(29) Miller, B. J., Culpepper, N., and Rapaport, M. H. (2014) C-reactive protein levels in schizophrenia: a review and meta-analysis. *Clin Schizophr Relat Psychoses.*, *7*, 223-230. doi: 210.3371/CSRP.MICU.020813. **R, C**

(37) Tonstad, S., and Cowan, J. L. (2009) C-reactive protein as a predictor of disease in smokers and former smokers: a review. *Int J Clin Pract.*, *63*, 1634-1641. doi: 1610.1111/j.1742-1241.2009.02179.x. Epub 02009 Aug 02129. **R, A, C, D, E, F**

(58) Koch, A., Fohlin, H., and Sorenson, S. (2009) Prognostic significance of C-reactive protein and smoking in patients with advanced non-small cell lung cancer treated with first-line palliative chemotherapy. *J Thorac Oncol.*, *4*, 326-332. doi: 310.1097/JTO.1090b1013e31819578c31819578. **D, C**

(76) Sin, D. D., Man, S. F., McWilliams, A., and Lam, S. (2006) Progression of airway dysplasia and C-reactive protein in smokers at high risk of lung cancer. *Am J Respir Crit Care Med.*, *173*, 535-539. Epub 2005 Dec 2009. **D, C**

(122) Alifano, M., Falcoz, P. E., Seegers, V., Roche, N., Schussler, O., Younes, M., Antonacci, F., Forgez, P., Dechartres, A., Massard, G., Damotte, D., and Regnard, J. F. (2011) Preresection serum C-reactive protein measurement and survival among patients with resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg.*, *142*, 1161-1167. doi: 1110.1016/j.jtcvs.2011.1107.1021. Epub 2011 Aug 1126. **C**

(123) Allin, K. H., Bojesen, S. E., Johansen, J. S., and Nordestgaard, B. G. (2012) Cancer risk by combined levels of YKL-40 and C-reactive protein in the general population. *Br J Cancer.*, *106*, 199-205. doi: 110.1038/bjc.2011.1501. Epub 2011 Nov 1017. **C**

(124) Allin, K. H., and Nordestgaard, B. G. (2011) Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci.*, *48*, 155-170. doi: 110.3109/10408363.10402011.10599831. **C, R**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(125) Douglas, J. B., Silverman, D. T., Weinstein, S. J., Graubard, B. I., Pollak, M. N., Tao, Y., Virtamo, J., Albanes, D., and Stolzenberg-Solomon, R. Z. (2011) Serum C-reactive protein and risk of pancreatic cancer in two nested, case-control studies. *Cancer Epidemiol Biomarkers Prev.*, *20*, 359-369. doi: 310.1158/1055-9965.EPI-1110-1024. Epub 2010 Dec 1120. **C**

(126) Guo, Y. Z., Pan, L., Du, C. J., Ren, D. Q., and Xie, X. M. (2013) Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. *Asian Pac J Cancer Prev*, *14*, 243-248. **C**

(127) Heikkila, K., Silander, K., Salomaa, V., Jousilahti, P., Koskinen, S., Pukkala, E., and Perola, M. (2011) C-reactive protein-associated genetic variants and cancer risk: findings from FINRISK 1992, FINRISK 1997 and Health 2000 studies. *Eur J Cancer.*, *47*, 404-412. doi: 410.1016/j.ejca.2010.1007.1032. Epub 2010 Aug 1018. **C**

(128) Hong, S., Kang, Y. A., Cho, B. C., and Kim, D. J. (2012) Elevated serum C-reactive protein as a prognostic marker in small cell lung cancer. *Yonsei Med J.*, *53*, 111-117. doi: 110.3349/ymj.2012.3353.3341.3111. **C**

(129) Kanoh, Y., Abe, T., Masuda, N., and Akahoshi, T. (2013) Progression of non-small cell lung cancer: diagnostic and prognostic utility of matrix metalloproteinase-2, C-reactive protein and serum amyloid A. *Oncol Rep.*, *29*, 469-473. doi: 410.3892/or.2012.2123. Epub 2012 Nov 3895. **C**

(130) Ko, Y. J., Kwon, Y. M., Kim, K. H., Choi, H. C., Chun, S. H., Yoon, H. J., Goh, E., Cho, B., and Park, M. (2012) High-sensitivity C-reactive protein levels and cancer mortality. *Cancer Epidemiol Biomarkers Prev.*, *21*, 2076-2086. doi: 2010.1158/1055-9965.EPI-2012-0611. **C**

(131) Kruse, A. L., Luebbers, H. T., and Gratz, K. W. (2010) C-reactive protein levels: a prognostic marker for patients with head and neck cancer? *Head Neck Oncol.*, *2:21.*, 10.1186/1758-3284-1182-1121. **C**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(132) Lukaszewicz-Zajac, M., Mroczko, B., and Szmitkowski, M. (2010) [The role of interleukin-6 and C-reactive protein in gastric cancer]. *Pol Merkur Lekarski.*, *29*, 382-386. **C**

(144) Vaguliene, N., Zemaitis, M., Miliauskas, S., Urboniene, D., Sitkauskiene, B., and Sakalauskas, R. (2011) Comparison of C-reactive protein levels in patients with lung cancer and chronic obstructive pulmonary disease. *Medicina (Kaunas)*, *47*, 421-427. Epub 2011 Nov 2018. **C, B**

(147) Zhou, B., Liu, J., Wang, Z. M., and Xi, T. (2012) C-reactive protein, interleukin 6 and lung cancer risk: a meta-analysis. *PLoS One*, *7*, e43075. doi: 43010.41371/journal.pone.0043075. Epub 0042012 Aug 0043017. **C**

(169) Tillett, W. S., and Francis, T. (1930) Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. *The Journal of experimental medicine*, *52*, 561-571. **C**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.5 Appendix 5 Inclusion criteria D

(1) Life Sciences Research Office (LSRO). (2007) *Biological effects assessment in the evaluation of potential reduced-risk tobacco products*. Bethesda, Maryland, USA. **R, A, D, E, F**

(2) US Department of Health and Human Services. (2010) *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*

A Report of the Surgeon General. **R, A, D, F**

(4) Bakhru, A., and Erlinger, T. P. (2005) Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. *PLoS Med.*, *2*, e160. Epub 2005 Jun 2028. **D, E, F**

(5) Benowitz, N. L., Fitzgerald, G. A., Wilson, M., and Zhang, Q. (1993) Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. *Journal of the American College of Cardiology*, *22*, 1159-1167. **D, G**

(13) Joseph, A. M., Hecht, S. S., Murphy, S. E., Lando, H., Carmella, S. G., Gross, M., Bliss, R., Le, C. T., and Hatsukami, D. K. (2008) Smoking reduction fails to improve clinical and biological markers of cardiac disease: a randomized controlled trial. *Nicotine Tob Res.*, *10*, 471-481. doi: 410.1080/14622200801901948. **D, E, F**

(15) Ohsawa, M., Okayama, A., Nakamura, M., Onoda, T., Kato, K., Itai, K., Yoshida, Y., Ogawa, A., Kawamura, K., and Hiramori, K. (2005) CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. *Prev Med.*, *41*, 651-656. **D, E, F**

(20) Tracy, R. P., Psaty, B. M., Macy, E., Bovill, E. G., Cushman, M., Cornell, E. S., and Kuller, L. H. (1997) Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol.*, *17*, 2167-2176. **D, E, F**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(24) Wannamethee, S. G., Lowe, G. D., Shaper, A. G., Rumley, A., Lennon, L., and Whincup, P. H. (2005) Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur Heart J.*, *26*, 1765-1773. Epub 2005 Apr 1767. **D**

(37) Tonstad, S., and Cowan, J. L. (2009) C-reactive protein as a predictor of disease in smokers and former smokers: a review. *Int J Clin Pract.*, *63*, 1634-1641. doi: 1610.1111/j.1742-1241.2009.02179.x. Epub 02009 Aug 02129. **R, A, C, D, E, F**

(39) Ahonen, T. M., Kautiainen, H. J., Keinanen-Kiukaanniemi, S. M., Kumpusalo, E. A., and Vanhala, M. J. (2008) Gender difference among smoking, adiponectin, and high-sensitivity C-reactive protein. *Am J Prev Med.*, *35*, 598-601. doi: 510.1016/j.amepre.2008.1009.1011. Epub 2008 Oct 1018. **D, E, F, A**

(40) Aksu, F., Capan, N., Aksu, K., Ofluoglu, R., Canbakan, S., Yavuz, B., and Akin, K. O. (2013) C-reactive protein levels are raised in stable Chronic obstructive pulmonary disease patients independent of smoking behavior and biomass exposure. *J Thorac Dis.*, *5*, 414-421. doi: 410.3978/j.issn.2072-1439.2013.3906.3927. **D, B**

(42) Alyan, O., Kacmaz, F., Ozdemir, O., Karahan, Z., Taskesen, T., Iyem, H., Alan, S., Karadede, A., and Ilkay, E. (2008) [High levels of high-sensitivity C-reactive protein and impaired autonomic activity in smokers]. *Turk Kardiyol Dern Ars.*, *36*, 368-375. **D, E**

(43) Azar, R., and Richard, A. (2011) Elevated salivary C-reactive protein levels are associated with active and passive smoking in healthy youth: A pilot study. *J Inflamm (Lond). 8*, 37. doi: 10.1186/1476-9255-1188-1137. **D, E**

(48) Feng, D., Liu, T., Wang, H., Karp, E., Ling, W., and Chen, W. Q. (2014) Mediation role of C-reactive protein on the association between smoking quantity and type 2 diabetes in current Chinese smokers. *J Diabetes Res*, *2014:171538.*, 10.1155/2014/171538. Epub 172014 Jul 171533. **D, E**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(49) Hanyu, O., Yoshida, J., Abe, E., Hirayama, S., Miyake, K., Aizawa, Y., and Miida, T. (2009) High-sensitivity CRP reflects insulin resistance in smokers. *J Atheroscler Thromb.*, *16*, 560-567. Epub 2009 Sep 2014. **D**

(50) Hastie, C. E., Haw, S., and Pell, J. P. (2008) Impact of smoking cessation and lifetime exposure on C-reactive protein. *Nicotine Tob Res.*, *10*, 637-642. doi: 610.1080/14622200801978722. **D, E, F**

(54) Kawada, T. (2015) Relationships between the smoking status and plasma fibrinogen, white blood cell count and serum C-reactive protein in Japanese workers. *Diabetes Metab Syndr*, *6*, 00023-00025. **D, E, F**

(55) Khand, F., Shaikh, S. S., Ata, M. A., and Shaikh, S. S. (2015) Evaluation of the effect of smoking on complete blood counts, serum C-reactive protein and magnesium levels in healthy adult male smokers. *J Pak Med Assoc.*, *65*, 59-61. **D**

(56) Khoo, C. M., Tan, M., Wu, Y., Wai, C. H., Subramaniam, T., Lee, J., and Tai, E. S. (2011) Central obesity and smoking are key modifiable risk factors for elevated C-reactive protein in Asian individuals who are not eligible for statin therapy. *Nutr Diabetes.*, *1:e8.*, 10.1038/nutd.2011.1034. **D, F**

(57) Kleber, M. E., Siekmeier, R., Delgado, G., Grammer, T. B., Winkelmann, B. R., Scharnagl, H., Boehm, B. O., and Marz, W. (2015) C-reactive protein and lipoprotein-associated phospholipase A2 in smokers and nonsmokers of the Ludwigshafen Risk and Cardiovascular Health study. *Adv Exp Med Biol*, *832:15-23.*, 10.1007/5584_2014_1006. **D**

(58) Koch, A., Fohlin, H., and Sorenson, S. (2009) Prognostic significance of C-reactive protein and smoking in patients with advanced non-small cell lung cancer treated with first-line palliative chemotherapy. *J Thorac Oncol.*, *4*, 326-332. doi: 310.1097/JTO.1090b1013e31819578c31819578. **D, C**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(61) Le-Ha, C., Beilin, L. J., Burrows, S., Oddy, W. H., Hands, B., and Mori, T. A. (2014) Gender and the active smoking and high-sensitivity C-reactive protein relation in late adolescence. *J Lipid Res.*, *55*, 758-764. doi: 710.1194/jlr.P045369. Epub 042014 Feb 045327. **D**

(63) Madsen, C., Nafstad, P., Eikvar, L., Schwarze, P. E., Ronningen, K. S., and Haaheim, L. L. (2007) Association between tobacco smoke exposure and levels of C-reactive protein in the Oslo II Study. *Eur J Epidemiol*, *22*, 311-317. Epub 2007 May 2005. **D, E, F**

(64) Mao, J., Liu, J., Pang, X., Li, M., Song, J., Han, C., Wu, D., and Wang, S. (2012) Nicotine induces the expression of C-reactive protein via MAPK-dependent signal pathway in U937 macrophages. *Mol Cells.*, *34*, 457-461. doi: 410.1007/s10059-10012-10205-10050. Epub 12012 Nov 10056. **D**

(65) Martin de Diego, C. E., Gomez de Terreros Sanchez, F. J., Caro de Miguel, M. C., Medina Font, J., Matesanz Ruiz, C., and Gomez de Terreros Caro, J. (2006) [C-reactive protein value related to a smoking history and composition of nicotine and tobacco tar]. *An Med Interna.*, *23*, 3-10. **D, E, F**

(66) Melbye, H., Halvorsen, D. S., Hartz, I., Medbo, A., Brox, J., Eggen, A. E., and Njolstad, I. (2007) Bronchial airflow limitation, smoking, body mass index, and statin use are strongly associated with the C-reactive protein level in the elderly. The Tromso Study 2001. *Respir Med.*, *101*, 2541-2549. Epub 2007 Sep 2546. **D, B**

(67) Merghani, T. H., Saeed, A., and Alawad, A. (2012) Changes in plasma IL4, TNFa and CRP in response to regular passive smoking at home among healthy school children in Khartoum, Sudan. *Afr Health Sci.*, *12*, 41-47. **D**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(69) O'Callaghan, P. A., Fitzgerald, A., Fogarty, J., Gaffney, P., Hanbidge, M., Boran, G., Enright, H., Murphy, J., McCarthy, B., and Graham, I. M. (2005) New and old cardiovascular risk factors: C-reactive protein, homocysteine, cysteine and von Willebrand factor increase risk, especially in smokers. *Eur J Cardiovasc Prev Rehabil.*, *12*, 542-547. **D, A**

(70) Ohsawa, M., Itai, K., Onoda, T., Tanno, K., Sasaki, S., Nakamura, M., Ogawa, A., Sakata, K., Kawamura, K., Kuribayashi, T., Yoshida, Y., and Okayama, A. (2008) Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers. *Atherosclerosis.*, *201*, 184-191. doi: 110.1016/j.atherosclerosis.2008.1001.1008. Epub 2008 Mar 1017. **D**

(71) O'Loughlin, J., Lambert, M., Karp, I., McGrath, J., Gray-Donald, K., Barnett, T. A., Delvin, E. E., Levy, E., and Paradis, G. (2008) Association between cigarette smoking and C-reactive protein in a representative, population-based sample of adolescents. *Nicotine Tob Res.*, *10*, 525-532. doi: 510.1080/14622200801901997. **D, E**

(72) Pinto-Plata, V. M., Mullerova, H., Toso, J. F., Feudjo-Tepie, M., Soriano, J. B., Vessey, R. S., and Celli, B. R. (2006) C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax.*, *61*, 23-28. Epub 2005 Sep 2002. **D, B**

(73) Saijo, Y., Yoshioka, E., Fukui, T., Kawaharada, M., Sata, F., Sato, H., and Kishi, R. (2007) Effects of the Interaction between Interleukin-6 -634C/G Polymorphism and Smoking on Serum C-Reactive Protein Concentrations. *Hypertens Res.*, *30*, 593-599.

(74) Sauriasari, R., Sakano, N., Wang, D. H., Takaki, J., Takemoto, K., Wang, B., **D**

(76) Sin, D. D., Man, S. F., McWilliams, A., and Lam, S. (2006) Progression of airway dysplasia and C-reactive protein in smokers at high risk of lung cancer. *Am J Respir Crit Care Med.*, *173*, 535-539. Epub 2005 Dec 2009. **D, C**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(95) Out, D., Hall, R. J., Granger, D. A., Page, G. G., and Woods, S. J. (2012) Assessing salivary C-reactive protein: longitudinal associations with systemic inflammation and cardiovascular disease risk in women exposed to intimate partner violence. *Brain Behav Immun.*, *26*, 543-551. doi: 510.1016/j.bbi.2012.1001.1019. Epub 2012 Feb 1012. **A, D**

(148) Bazzano, L. A., He, J., Muntner, P., Vupputuri, S., and Whelton, P. K. (2003) Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med.*, *138*, 891-897. **D, E, F**

(149) Bermudez, E. A., Rifai, N., Buring, J., Manson, J. E., and Ridker, P. M. (2002) Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. *Arterioscler Thromb Vasc Biol.*, *22*, 1668-1673. **D, F**

(150) Calapai, G., Caputi, A. P., Mannucci, C., Gregg, E. O., Pieratti, A., Aurora, R. G., Chaudhary, N., Puntoni, R., Lowe, F., McEwan, M., Bassi, A., Morandi, S., and Nunziata, A. (2009) A cross-sectional investigation of biomarkers of risk after a decade of smoking. *Inhal.Toxicol.*, *21*, 1138-1143. **D**

(151) Crook, M. A., Scott, D. A., Stapleton, J. A., Palmer, R. M., Wilson, R. F., and Sutherland, G. (2000) Circulating concentrations of C-reactive protein and total sialic acid in tobacco smokers remain unchanged following one year of validated smoking cessation. *Eur J Clin Invest.*, *30*, 861-865. **D, E, F**

(152) Fredrikson, G. N., Hedblad, B., Nilsson, J. A., Alm, R., Berglund, G., and Nilsson, J. (2004) Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma C-reactive protein levels. *Metabolism.*, *53*, 1436-1442. **D**

(153) Frohlich, M., Sund, M., Lowel, H., Imhof, A., Hoffmeister, A., and Koenig, W. (2003) Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). *Eur Heart J.*, *24*, 1365-1372. **D, E, F**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(154) Frost-Pineda, K., Liang, Q., Liu, J., Rimmer, L., Jin, Y., Feng, S., Kapur, S., Mendes, P., Roethig, H., and Sarkar, M. (2011) Biomarkers of Potential Harm Among Adult Smokers and Nonsmokers in the Total Exposure Study. *Nicotine.Tob.Res.*, *13*, 182-193. **D**

(155) Garcia-Lorda, P., Bullo, M., Balanza, R., and Salas-Salvado, J. (2006) C-reactive protein, adiposity and cardiovascular risk factors in a Mediterranean population. *Int J Obes (Lond).* *30*, 468-474. **D, A**

(156) Helmersson, J., Larsson, A., Vessby, B., and Basu, S. (2005) Active smoking and a history of smoking are associated with enhanced prostaglandin F(2alpha), interleukin-6 and F2-isoprostane formation in elderly men. *Atherosclerosis.*, *181*, 201-207. Epub 2005 Apr 2026. **D, F, A**

(157) Kiechl, S., Werner, P., Egger, G., Oberhollenzer, F., Mayr, M., Xu, Q., Poewe, W., and Willeit, J. (2002) Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. *Stroke.*, *33*, 2170-2176. **D, E, F**

(158) Koenig, W., Sund, M., Frohlich, M., Fischer, H. G., Lowel, H., Doring, A., Hutchinson, W. L., and Pepys, M. B. (1999) C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation.*, *99*, 237-242. **D, A**

(160) Lavi, S., Prasad, A., Yang, E. H., Mathew, V., Simari, R. D., Rihal, C. S., Lerman, L. O., and Lerman, A. (2007) Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. *Circulation.*, *115*, 2621-2627. Epub 2007 May 2627. **D, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(161) Levitzky, Y. S., Guo, C. Y., Rong, J., Larson, M. G., Walter, R. E., Keaney, J. F., Jr., Sutherland, P. A., Vasan, A., Lipinska, I., Evans, J. C., and Benjamin, E. J. (2008) Relation of smoking status to a panel of inflammatory markers: the framingham offspring. *Atherosclerosis.*, *201*, 217-224. doi: 210.1016/j.atherosclerosis.2007.1012.1058. Epub 2008 Mar 1014. **D, F**

(162) Lowe, G. D., Yarnell, J. W., Rumley, A., Bainton, D., and Sweetnam, P. M. (2001) C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis? *Arterioscler Thromb Vasc Biol.*, *21*, 603-610. **D, E, F, A**

(163) Mendall, M. A., Patel, P., Ballam, L., Strachan, D., and Northfield, T. C. (1996) C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *BMJ.*, *312*, 1061-1065. **D, A**

(164) Panagiotakos, D. B., Pitsavos, C., Chrysohoou, C., Skoumas, J., Masoura, C., Toutouzas, P., and Stefanadis, C. (2004) Effect of exposure to secondhand smoke on markers of inflammation: the ATTICA study. *Am J Med.*, *116*, 145-150. **D, F**

(165) Pirkola, J., Vaarasmaki, M., Ala-Korpela, M., Bloigu, A., Canoy, D., Hartikainen, A. L., Leinonen, M., Miettola, S., Paldanius, M., Tammelin, T. H., Jarvelin, M. R., and Pouta, A. (2010) Low-grade, systemic inflammation in adolescents: association with early-life factors, gender, and lifestyle. *Am J Epidemiol.*, *171*, 72-82. doi: 10.1093/aje/kwp1320. Epub 2009 Nov 1016. **D**

(166) Roethig, H. J., Feng, S., Liang, Q., Liu, J., Rees, W. A., and Zedler, B. K. (2008) A 12-Month, Randomized, Controlled Study to Evaluate Exposure and Cardiovascular Risk Factors in Adult Smokers Switching From Conventional Cigarettes to a Second-Generation Electrically Heated Cigarette Smoking System. *J.Clin.Pharmacol.*, *48*, 580-591. **D, G**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(167) Rohde, L. E., Hennekens, C. H., and Ridker, P. M. (1999) Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol.*, *84*, 1018-1022. **D, E, F, A**

(168) Yamada, S., Gotoh, T., Nakashima, Y., Kayaba, K., Ishikawa, S., Nago, N., Nakamura, Y., Itoh, Y., and Kajii, E. (2001) Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population : Jichi Medical School Cohort Study. *Am J Epidemiol.*, *153*, 1183-1190. **D**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.6 Appendix 6 Inclusion criteria E

(1) Life Sciences Research Office (LSRO). (2007) *Biological effects assessment in the evaluation of potential reduced-risk tobacco products*. Bethesda, Maryland, USA. **R, A, D, E, F**

(4) Bakhru, A., and Erlinger, T. P. (2005) Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. *PLoS Med.*, *2*, e160. Epub 2005 Jun 2028. **D, E, F**

(13) Joseph, A. M., Hecht, S. S., Murphy, S. E., Lando, H., Carmella, S. G., Gross, M., Bliss, R., Le, C. T., and Hatsukami, D. K. (2008) Smoking reduction fails to improve clinical and biological markers of cardiac disease: a randomized controlled trial. *Nicotine Tob Res.*, *10*, 471-481. doi: 410.1080/14622200801901948. **D, E, F**

(15) Ohsawa, M., Okayama, A., Nakamura, M., Onoda, T., Kato, K., Itai, K., Yoshida, Y., Ogawa, A., Kawamura, K., and Hiramori, K. (2005) CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. *Prev Med.*, *41*, 651-656. **D, E, F**

(20) Tracy, R. P., Psaty, B. M., Macy, E., Bovill, E. G., Cushman, M., Cornell, E. S., and Kuller, L. H. (1997) Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol.*, *17*, 2167-2176. **D, E, F**

(39) Ahonen, T. M., Kautiainen, H. J., Keinanen-Kiukaanniemi, S. M., Kumpusalo, E. A., and Vanhala, M. J. (2008) Gender difference among smoking, adiponectin, and high-sensitivity C-reactive protein. *Am J Prev Med.*, *35*, 598-601. doi: 510.1016/j.amepre.2008.1009.1011. Epub 2008 Oct 1018. **D, E, F, A**

(42) Alyan, O., Kacmaz, F., Ozdemir, O., Karahan, Z., Taskesen, T., Iyem, H., Alan, S., Karadede, A., and Ilkay, E. (2008) [High levels of high-sensitivity C-reactive protein and impaired autonomic activity in smokers]. *Turk Kardiyol Dern Ars.*, *36*, 368-375. **D, E**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(43) Azar, R., and Richard, A. (2011) Elevated salivary C-reactive protein levels are associated with active and passive smoking in healthy youth: A pilot study. *J Inflamm (Lond). 8*, 37. doi: 10.1186/1476-9255-1188-1137. **D, E**

(48) Feng, D., Liu, T., Wang, H., Karp, E., Ling, W., and Chen, W. Q. (2014) Mediation role of C-reactive protein on the association between smoking quantity and type 2 diabetes in current Chinese smokers. *J Diabetes Res*, *2014:171538.*, 10.1155/2014/171538. Epub 172014 Jul 171533. **D, E**

(50) Hastie, C. E., Haw, S., and Pell, J. P. (2008) Impact of smoking cessation and lifetime exposure on C-reactive protein. *Nicotine Tob Res.*, *10*, 637-642. doi: 610.1080/14622200801978722. **D, E, F**

(54) Kawada, T. (2015) Relationships between the smoking status and plasma fibrinogen, white blood cell count and serum C-reactive protein in Japanese workers. *Diabetes Metab Syndr*, *6*, 00023-00025. **D, E, F**

(63) Madsen, C., Nafstad, P., Eikvar, L., Schwarze, P. E., Ronningen, K. S., and Haaheim, L. L. (2007) Association between tobacco smoke exposure and levels of C-reactive protein in the Oslo II Study. *Eur J Epidemiol*, *22*, 311-317. Epub 2007 May 2005. **D, E, F**

(65) Martin de Diego, C. E., Gomez de Terreros Sanchez, F. J., Caro de Miguel, M. C., Medina Font, J., Matesanz Ruiz, C., and Gomez de Terreros Caro, J. (2006) [C-reactive protein value related to a smoking history and composition of nicotine and tobacco tar]. *An Med Interna.*, *23*, 3-10. **D, E, F**

(71) O'Loughlin, J., Lambert, M., Karp, I., McGrath, J., Gray-Donald, K., Barnett, T. A., Delvin, E. E., Levy, E., and Paradis, G. (2008) Association between cigarette smoking and C-reactive protein in a representative, population-based sample of adolescents. *Nicotine Tob Res.*, *10*, 525-532. doi: 510.1080/14622200801901997. **D, E**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(148) Bazzano, L. A., He, J., Muntner, P., Vupputuri, S., and Whelton, P. K. (2003) Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med.*, *138*, 891-897. **D, E, F**

(151) Crook, M. A., Scott, D. A., Stapleton, J. A., Palmer, R. M., Wilson, R. F., and Sutherland, G. (2000) Circulating concentrations of C-reactive protein and total sialic acid in tobacco smokers remain unchanged following one year of validated smoking cessation. *Eur J Clin Invest.*, *30*, 861-865. **D, E, F**

(153) Frohlich, M., Sund, M., Lowel, H., Imhof, A., Hoffmeister, A., and Koenig, W. (2003) Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). *Eur Heart J.*, *24*, 1365-1372. **D, E, F**

(157) Kiechl, S., Werner, P., Egger, G., Oberhollenzer, F., Mayr, M., Xu, Q., Poewe, W., and Willeit, J. (2002) Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. *Stroke.*, *33*, 2170-2176. **D, E, F**

(162) Lowe, G. D., Yarnell, J. W., Rumley, A., Bainton, D., and Sweetnam, P. M. (2001) C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis? *Arterioscler Thromb Vasc Biol.*, *21*, 603-610. **D, E, F, A**

(167) Rohde, L. E., Hennekens, C. H., and Ridker, P. M. (1999) Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol.*, *84*, 1018-1022. **D, E, F, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.7 Appendix 7 Inclusion criteria F

(1) Life Sciences Research Office (LSRO). (2007) *Biological effects assessment in the evaluation of potential reduced-risk tobacco products*. Bethesda, Maryland, USA. **R, A, D, E, F**

(2) US Department of Health and Human Services. (2010) *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*

A Report of the Surgeon General. **R, A, D, F**

(4) Bakhru, A., and Erlinger, T. P. (2005) Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. *PLoS Med.*, *2*, e160. Epub 2005 Jun 2028. **D, E, F**

(13) Joseph, A. M., Hecht, S. S., Murphy, S. E., Lando, H., Carmella, S. G., Gross, M., Bliss, R., Le, C. T., and Hatsukami, D. K. (2008) Smoking reduction fails to improve clinical and biological markers of cardiac disease: a randomized controlled trial. *Nicotine Tob Res.*, *10*, 471-481. doi: 410.1080/14622200801901948. **D, E, F**

(15) Ohsawa, M., Okayama, A., Nakamura, M., Onoda, T., Kato, K., Itai, K., Yoshida, Y., Ogawa, A., Kawamura, K., and Hiramori, K. (2005) CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. *Prev Med.*, *41*, 651-656. **D, E, F**

(20) Tracy, R. P., Psaty, B. M., Macy, E., Bovill, E. G., Cushman, M., Cornell, E. S., and Kuller, L. H. (1997) Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol.*, *17*, 2167-2176. **D, E, F**

(37) Tonstad, S., and Cowan, J. L. (2009) C-reactive protein as a predictor of disease in smokers and former smokers: a review. *Int J Clin Pract.*, *63*, 1634-1641. doi: 1610.1111/j.1742-1241.2009.02179.x. Epub 02009 Aug 02129. **R, A, C, D, E, F**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(39) Ahonen, T. M., Kautiainen, H. J., Keinanen-Kiukaanniemi, S. M., Kumpusalo, E. A., and Vanhala, M. J. (2008) Gender difference among smoking, adiponectin, and high-sensitivity C-reactive protein. *Am J Prev Med.*, *35*, 598-601. doi: 510.1016/j.amepre.2008.1009.1011. Epub 2008 Oct 1018. **D, E, F, A**

(50) Hastie, C. E., Haw, S., and Pell, J. P. (2008) Impact of smoking cessation and lifetime exposure on C-reactive protein. *Nicotine Tob Res.*, *10*, 637-642. doi: 610.1080/14622200801978722. **D, E, F**

(54) Kawada, T. (2015) Relationships between the smoking status and plasma fibrinogen, white blood cell count and serum C-reactive protein in Japanese workers. *Diabetes Metab Syndr*, *6*, 00023-00025. **D, E, F**

(56) Khoo, C. M., Tan, M., Wu, Y., Wai, C. H., Subramaniam, T., Lee, J., and Tai, E. S. (2011) Central obesity and smoking are key modifiable risk factors for elevated C-reactive protein in Asian individuals who are not eligible for statin therapy. *Nutr Diabetes.*, *1:e8.*, 10.1038/nutd.2011.1034. **D, F**

(63) Madsen, C., Nafstad, P., Eikvar, L., Schwarze, P. E., Ronningen, K. S., and Haaheim, L. L. (2007) Association between tobacco smoke exposure and levels of C-reactive protein in the Oslo II Study. *Eur J Epidemiol*, *22*, 311-317. Epub 2007 May 2005. **D, E, F**

(65) Martin de Diego, C. E., Gomez de Terreros Sanchez, F. J., Caro de Miguel, M. C., Medina Font, J., Matesanz Ruiz, C., and Gomez de Terreros Caro, J. (2006) [C-reactive protein value related to a smoking history and composition of nicotine and tobacco tar]. *An Med Interna.*, *23*, 3-10. **D, E, F**

(148) Bazzano, L. A., He, J., Muntner, P., Vupputuri, S., and Whelton, P. K. (2003) Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med.*, *138*, 891-897. **D, E, F**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(149) Bermudez, E. A., Rifai, N., Buring, J., Manson, J. E., and Ridker, P. M. (2002) Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. *Arterioscler Thromb Vasc Biol.*, *22*, 1668-1673. **D, F**

(151) Crook, M. A., Scott, D. A., Stapleton, J. A., Palmer, R. M., Wilson, R. F., and Sutherland, G. (2000) Circulating concentrations of C-reactive protein and total sialic acid in tobacco smokers remain unchanged following one year of validated smoking cessation. *Eur J Clin Invest.*, *30*, 861-865. **D, E, F**

(153) Frohlich, M., Sund, M., Lowel, H., Imhof, A., Hoffmeister, A., and Koenig, W. (2003) Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). *Eur Heart J.*, *24*, 1365-1372. **D, E, F**

(156) Helmersson, J., Larsson, A., Vessby, B., and Basu, S. (2005) Active smoking and a history of smoking are associated with enhanced prostaglandin F(2alpha), interleukin-6 and F2-isoprostane formation in elderly men. *Atherosclerosis.*, *181*, 201-207. Epub 2005 Apr 2026. **D, F, A**

(157) Kiechl, S., Werner, P., Egger, G., Oberhollenzer, F., Mayr, M., Xu, Q., Poewe, W., and Willeit, J. (2002) Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. *Stroke.*, *33*, 2170-2176. **D, E, F**

(161) Levitzky, Y. S., Guo, C. Y., Rong, J., Larson, M. G., Walter, R. E., Keaney, J. F., Jr., Sutherland, P. A., Vasan, A., Lipinska, I., Evans, J. C., and Benjamin, E. J. (2008) Relation of smoking status to a panel of inflammatory markers: the framingham offspring. *Atherosclerosis.*, *201*, 217-224. doi: 210.1016/j.atherosclerosis.2007.1012.1058. Epub 2008 Mar 1014. **D, F**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(162) Lowe, G. D., Yarnell, J. W., Rumley, A., Bainton, D., and Sweetnam, P. M. (2001) C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis? *Arterioscler Thromb Vasc Biol.*, *21*, 603-610. **D, E, F, A**

(164) Panagiotakos, D. B., Pitsavos, C., Chrysohoou, C., Skoumas, J., Masoura, C., Toutouzas, P., and Stefanadis, C. (2004) Effect of exposure to secondhand smoke on markers of inflammation: the ATTICA study. *Am J Med.*, *116*, 145-150. **D, F**

(167) Rohde, L. E., Hennekens, C. H., and Ridker, P. M. (1999) Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol.*, *84*, 1018-1022. **D, E, F, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.8 Appendix 8 Inclusion criteria G

(5) Benowitz, N. L., Fitzgerald, G. A., Wilson, M., and Zhang, Q. (1993) Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. *Journal of the American College of Cardiology*, *22*, 1159-1167. **D, G**

(166) Roethig, H. J., Feng, S., Liang, Q., Liu, J., Rees, W. A., and Zedler, B. K. (2008) A 12-Month, Randomized, Controlled Study to Evaluate Exposure and Cardiovascular Risk Factors in Adult Smokers Switching From Conventional Cigarettes to a Second-Generation Electrically Heated Cigarette Smoking System. *J.Clin.Pharmacol.*, *48*, 580-591. **D, G**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.9 Appendix 9 Review articles

(1) Life Sciences Research Office (LSRO). (2007) *Biological effects assessment in the evaluation of potential reduced-risk tobacco products*. Bethesda, Maryland, USA. **R, A, D, E, F**

(2) US Department of Health and Human Services. (2010) *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*

A Report of the Surgeon General. **R, A, D, F**

(25) Corrado, E., and Novo, S. (2007) [High sensitivity of C-reactive protein in primary prevention]. *G Ital Cardiol (Rome). 8*, 327-334. **R, A**

(26) Fabijanic, D., Banic, M., and Kardum, D. (2006) [C-reactive protein in cardiovascular risk evaluation]. *Lijec Vjesn.*, *128*, 167-174. **R, A**

(27) Hemingway, H., Philipson, P., Chen, R., Fitzpatrick, N. K., Damant, J., Shipley, M., Abrams, K. R., Moreno, S., McAllister, K. S., Palmer, S., Kaski, J. C., Timmis, A. D., and Hingorani, A. D. (2010) Evaluating the quality of research into a single prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. *PLoS Med.*, *7*, e1000286. doi: 1000210.1001371/journal.pmed.1000286. **R, A**

(28) Kao, P. C., Shiesh, S. C., and Wu, T. J. (2006) Serum C-reactive protein as a marker for wellness assessment. *Ann Clin Lab Sci.*, *36*, 163-169. **R, A**

(29) Miller, B. J., Culpepper, N., and Rapaport, M. H. (2014) C-reactive protein levels in schizophrenia: a review and meta-analysis. *Clin Schizophr Relat Psychoses.*, *7*, 223-230. doi: 210.3371/CSRP.MICU.020813. **R, C**

(30) Nanri, A., Moore, M. A., and Kono, S. (2007) Impact of C-reactive protein on disease risk and its relation to dietary factors. *Asian Pac J Cancer Prev.*, *8*, 167-177. **R**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(31) Plaisance, E. P., and Grandjean, P. W. (2006) Physical activity and high-sensitivity C-reactive protein. *Sports Med*, *36*, 443-458. **R**

(32) Ridker, P. M. (2007) C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol.*, *49*, 2129-2138. Epub 2007 Apr 2130. **R, A**

(33) Ridker, P. M., and Silvertown, J. D. (2008) Inflammation, C-reactive protein, and atherothrombosis. *J Periodontol.*, *79*, 1544-1551. doi: 1510.1902/jop.2008.080249. **R, A**

(34) Rodrigues, I. M., and Klein, L. C. (2006) Boiled or filtered coffee? Effects of coffee and caffeine on cholesterol, fibrinogen and C-reactive protein. *Toxicol Rev*, *25*, 55-69. **R, A**

(35) Rudolf, J., and Lewandrowski, K. B. (2014) Cholesterol, lipoproteins, high-sensitivity c-reactive protein, and other risk factors for atherosclerosis. *Clin Lab Med*, *2014 Mar;34*, 113-127. **R, A**

(36) Shah, T., Newcombe, P., Smeeth, L., Addo, J., Casas, J. P., Whittaker, J., Miller, M. A., Tinworth, L., Jeffery, S., Strazzullo, P., Cappuccio, F. P., and Hingorani, A. D. (2010) Ancestry as a determinant of mean population C-reactive protein values: implications for cardiovascular risk prediction. *Circ Cardiovasc Genet.*, *3*, 436-444. doi: 410.1161/CIRCGENETICS.1110.957431. Epub 952010 Sep 957428. **R**

(37) Tonstad, S., and Cowan, J. L. (2009) C-reactive protein as a predictor of disease in smokers and former smokers: a review. *Int J Clin Pract.*, *63*, 1634-1641. doi: 1610.1111/j.1742-1241.2009.02179.x. Epub 02009 Aug 02129. **R, A, C, D, E, F**

(38) Yosef-Levi, I. M., Grad, E., and Danenberg, H. D. (2007) [C-reactive protein and atherothrombosis--a prognostic factor or a risk factor?]. *Harefuah*, *2007 Dec;146*, 970-974. **R, A**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(104) Yousuf, O., Mohanty, B. D., Martin, S. S., Joshi, P. H., Blaha, M. J., Nasir, K., Blumenthal, R. S., and Budoff, M. J. (2013) High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? *J Am Coll Cardiol.*, *62*, 397-408. doi: 310.1016/j.jacc.2013.1005.1016. Epub 2013 May 1030. **A, R**

(124) Allin, K. H., and Nordestgaard, B. G. (2011) Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci.*, *48*, 155-170. doi: 110.3109/10408363.10402011.10599831. **C, R**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.10 Appendix 10 Excluded articles

(3) Axelsson, T., Jansson, P. A., Smith, U., and Eliasson, B. (2001) Nicotine infusion acutely impairs insulin sensitivity in type 2 diabetic patients but not in healthy subjects. *J Intern Med.*, *249*, 539-544. **01**

(11) Jensen, E. J., Pedersen, B., Frederiksen, R., and Dahl, R. (1998) Prospective study on the effect of smoking and nicotine substitution on leucocyte blood counts and relation between blood leucocytes and lung function. *Thorax.*, *53*, 784-789. **01**

(21) Tuut, M., and Hense, H. W. (2001) Smoking, other risk factors and fibrinogen levels. evidence of effect modification. *Ann Epidemiol.*, *11*, 232-238. **01**

(12) Joseph, A. M., Hecht, S. S., Murphy, S. E., Carmella, S. G., Le, C. T., Zhang, Y., Han, S., and Hatsukami, D. K. (2005) Relationships between cigarette consumption and biomarkers of tobacco toxin exposure. *Cancer Epidemiol Biomarkers Prev.*, *14*, 2963-2968. **01**

(102) Wannamethee, S. G., Welsh, P., Lowe, G. D., Gudnason, V., Di Angelantonio, E., Lennon, L., Rumley, A., Whincup, P. H., and Sattar, N. (2011) N-terminal pro-brain natriuretic Peptide is a more useful predictor of cardiovascular disease risk than C-reactive protein in older men with and without pre-existing cardiovascular disease. *J Am Coll Cardiol.*, *58*, 56-64. doi: 10.1016/j.jacc.2011.1002.1041. **01**

(8) Chakraborti, T., Mandal, A., Mandal, M., Das, S., and Chakraborti, S. (2000) Complement activation in heart diseases. Role of oxidants. *Cell Signal.*, *12*, 607-617. **02**

(74) Sauriasari, R., Sakano, N., Wang, D. H., Takaki, J., Takemoto, K., Wang, B., **D** Sugiyama, H., Sato, Y., Takigawa, T., Takahashi, N., Kanbara, S., Hitomi, Y., Nakamura, H., and Ogino, K. (2010) C-reactive protein is associated with cigarette smoking-induced hyperfiltration and proteinuria in an apparently healthy population. *Hypertens Res.*, *33*, 1129-1136. doi: 1110.1038/hr.2010.1154. Epub 2010 Aug 1112. **02**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(75) Siedlinski, M., Klanderman, B., Sandhaus, R. A., Barker, A. F., Brantly, M. L., Eden, E., McElvaney, N. G., Rennard, S. I., Stocks, J. M., Stoller, J. K., Strange, C., Turino, G. M., Campbell, E. J., and Demeo, D. L. (2012) Association of cigarette smoking and CRP levels with DNA methylation in alpha-1 antitrypsin deficiency. *Epigenetics.*, *7*, 720-728. doi: 710.4161/epi.20319. Epub 22012 Jul 20311. **02**

(86) De Luca, A., de Gaetano Donati, K., Colafigli, M., Cozzi-Lepri, A., De Curtis, A., Gori, A., Sighinolfi, L., Giacometti, A., Capobianchi, M. R., D'Avino, A., Iacoviello, L., Cauda, R., and D'Arminio Monforte, A. (2013) The association of high-sensitivity c-reactive protein and other biomarkers with cardiovascular disease in patients treated for HIV: a nested case-control study. *BMC Infect Dis.*, *13:414.*, 10.1186/1471-2334-1113-1414. **02**

(91) Kones, R. (2010) Rosuvastatin, inflammation, C-reactive protein, JUPITER, and primary prevention of cardiovascular disease--a perspective. *Drug Des Devel Ther.*, *4:383-413.*, 10.2147/DDDT.S10812. **02**

(92) Koppolu, P., Durvasula, S., Palaparthy, R., Rao, M., Sagar, V., Reddy, S. K., and Lingam, S. (2013) Estimate of CRP and TNF-alpha level before and after periodontal therapy in cardiovascular disease patients. *Pan Afr Med J.*, *15:92.*, 10.11604/pamj.12013.11615.11692.12326. eCollection 12013. **02**

(96) Rahsepar, A. A., Mirzaee, A., Moodi, F., Moohebati, M., Tavallaie, S., Khorashadizadeh, F., Eshraghi, A., Alavi, M. S., Zarrabi, L., Sajjadian, M., Amini, M., Khojasteh, R., Paydar, R., Mousavi, S., Ghayour-Mobarhan, M., and Ferns, G. A. (2013) Changes in anti-heat shock protein 27 antibody and C-reactive protein levels following cardiac surgery and their association with cardiac function in patients with cardiovascular disease. *Cell Stress Chaperones.*, *18*, 65-74. doi: 10.1007/s12192-12012-10358-y. Epub 12012 Jul 12130. **02**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(115) Mezzomo, A., Bodin, O. L., Jr., and Lucia, V. (2011) Preoperative C-reactive protein predicts respiratory infection after coronary artery bypass graft surgery. *Arq Bras Cardiol.*, *97*, 365-371. Epub 2011 Sep 2030. **02**

(119) Rego, M. A., Martinez, F. E., Elias, J., and Mussi-Pinhata, M. M. (2010) Diagnostic value of interleukin-6 and C-reactive protein on early onset bacterial infection in preterm neonates with respiratory distress. *J Perinat Med.*, *38*, 527-533. doi: 510.1515/JPM.2010.1071. **02**

(133) Masago, K., Fujita, S., Togashi, Y., Kim, Y. H., Hatachi, Y., Fukuhara, A., Nagai, H., Irisa, K., Sakamori, Y., Okuda, C., Mio, T., and Mishima, M. (2010) Clinical significance of pretreatment C-reactive protein in patients with advanced nonsquamous, non-small cell lung cancer who received gefitinib. *Oncology*, *79*, 355-362. doi: 310.1159/000323486. Epub 000322011 Mar 000323424. **02**

(134) Matsumoto, T., Fujita, M., Hirota, T., Takeda, S., Hirano, R., Uchino, J., Harada, T., and Watanabe, K. (2013) Elevation of serum C-reactive protein predicts failure of the initial antimicrobial treatment for febrile neutropenia with lung cancer. *J Infect Chemother.*, *19*, 202-207. doi: 210.1007/s10156-10012-10474-10158. Epub 12012 Sep 10128. **02**

(135) Minamiya, Y., Miura, M., Hinai, Y., Saito, H., Ito, M., Imai, K., Ono, T., Motoyama, S., and Ogawa, J. (2010) The CRP 1846T/T genotype is associated with a poor prognosis in patients with non-small cell lung cancer. *Tumour Biol.*, *31*, 673-679. doi: 610.1007/s13277-13010-10086-13279. Epub 12010 Aug 13275. **02**

(136) O'Dowd, C., McRae, L. A., McMillan, D. C., Kirk, A., and Milroy, R. (2010) Elevated preoperative C-reactive protein predicts poor cancer specific survival in patients undergoing resection for non-small cell lung cancer. *J Thorac Oncol.*, *5*, 988-992. doi: 910.1097/JTO.1090b1013e3181da1078f1099. **02**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(137) Park, D. S., Kim, D., Hwang, K. E., Hwang, Y. R., Park, C., Seol, C. H., Cho, K. H., Kim, B. R., Park, S. H., Jeong, E. T., and Kim, H. R. (2013) Diagnostic value and prognostic significance of pleural C-reactive protein in lung cancer patients with malignant pleural effusions. *Yonsei Med J.*, *54*, 396-402. doi: 310.3349/ymj.2013.3354.3342.3396. **02**

(139) Shen, L., Li, Z. M., and Lu, S. (2011) [Clinical significance of C-reactive protein in patients with stage I non-small cell lung cancer]. *Zhonghua Zhong Liu Za Zhi.*, *33*, 442-446. **02**

(140) Srimuninnimit, V., Ariyapanya, S., Nimmannit, A., Wonglaksanapimon, S., Akewanlop, C., and Soparattanapaisarn, N. (2012) C-reactive protein as a monitor of chemotherapy response in advanced non-small cell lung cancer (CML study). *J Med Assoc Thai.*, *95*, S199-207. **02**

(141) Szkandera, J., Stotz, M., Absenger, G., Stojakovic, T., Samonigg, H., Kornprat, P., Schaberl-Moser, R., Alzoughbi, W., Lackner, C., Ress, A. L., Seggewies, F. S., Gerger, A., Hoefler, G., and Pichler, M. (2014) Validation of C-reactive protein levels as a prognostic indicator for survival in a large cohort of pancreatic cancer patients. *Br J Cancer.*, *110*, 183-188. doi: 110.1038/bjc.2013.1701. Epub 2013 Nov 1037. **02**

(142) Terata, K., Motoyama, S., Kamata, S., Hinai, Y., Miura, M., Sato, Y., Yoshino, K., Ito, A., Imai, K., Saito, H., and Minamiya, Y. (2014) Evaluation of the potential for lymph node metastasis using CRP 1846C>T genetic polymorphism in invasive breast cancer. *Tumour Biol.*, *35*, 5931-5935. doi: 5910.1007/s13277-13014-11786-13273. Epub 12014 Mar 13216. **02**

(143) Tomita, M., Shimizu, T., Ayabe, T., Nakamura, K., and Onitsuka, T. (2012) Elevated preoperative inflammatory markers based on neutrophil-to-lymphocyte ratio and C-reactive protein predict poor survival in resected non-small cell lung cancer. *Anticancer Res.*, *32*, 3535-3538. **02**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(145) Xu, M., Zhu, M., Du, Y., Yan, B., Wang, Q., Wang, C., and Zhao, J. (2013) Serum C-reactive protein and risk of lung cancer: a case-control study. *Med Oncol.*, *30*, 319. doi: 310.1007/s12032-12012-10319-12034. Epub 12012 Dec 12015. **02**

(146) Xu, Y., Li, Z., and Shen-Tu, Y. (2011) [The prognostic value of detection of serum C-reactive protein in the patients with stage I lung cancer]. *Zhongguo Fei Ai Za Zhi.*, *14*, 400-403. doi: 410.3779/j.issn.1009-3419.2011.3705.3704. **02**

(44) Cupul-Uicab, L. A., Skjaerven, R., Haug, K., Travlos, G. S., Wilson, R. E., Eggesbo, M., Hoppin, J. A., Whitworth, K. W., and Longnecker, M. P. (2012) Exposure to tobacco smoke in utero and subsequent plasma lipids, ApoB, and CRP among adult women in the MoBa cohort. *Environ Health Perspect.*, *120*, 1532-1537. doi: 1510.1289/ehp.1104563. Epub 1102012 Jul 1104519. **03**

(47) Fagerberg, B., Behre, C. J., Wikstrand, J., Hulten, L. M., and Hulthe, J. (2008) C-reactive protein and tumor necrosis factor-alpha in relation to insulin-mediated glucose uptake, smoking and atherosclerosis. *Scand J Clin Lab Invest*, *68*, 534-541. doi: 510.1080/00365510701870898. **03**

(51) Hatzis, G., Tousoulis, D., Papageorgiou, N., Bouras, G., Oikonomou, E., Miliou, A., Siasos, G., Toutouzas, K., Papaioannou, S., Tsiamis, E., Antoniades, C., and Stefanadis, C. (2014) Combined effects of smoking and interleukin-6 and C-reactive protein genetic variants on endothelial function, inflammation, thrombosis and incidence of coronary artery disease. *Int J Cardiol.*, *176*, 254-257. doi: 210.1016/j.ijcard.2014.1006.1058. Epub 2014 Jul 1015. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(52) Hilawe, E. H., Yatsuya, H., Li, Y., Uemura, M., Wang, C., Chiang, C., Toyoshima, H., Tamakoshi, K., Zhang, Y., Kawazoe, N., and Aoyama, A. (2015) Smoking and diabetes: is the association mediated by adiponectin, leptin, or C-reactive protein? *J Epidemiol*, *25*, 99-109. doi: 110.2188/jea.JE20140055. Epub 20142014 Nov 20140015. **03**

(53) Hung, M. Y., Hsu, K. H., Hung, M. J., Cheng, C. W., Kuo, L. T., and Cherng, W. J. (2009) Interaction between cigarette smoking and high-sensitivity C-reactive protein in the development of coronary vasospasm in patients without hemodynamically significant coronary artery disease. *Am J Med Sci.*, *338*, 440-446. doi: 410.1097/MAJ.1090b1013e3181b9147f. **03**

(59) Kodovazenitis, G., Pitsavos, C., Papadimitriou, L., Deliargyris, E. N., Vrotsos, I., Stefanadis, C., and Madianos, P. N. (2011) Periodontal disease is associated with higher levels of C-reactive protein in non-diabetic, non-smoking acute myocardial infarction patients. *J Dent.*, *39*, 849-854. doi: 810.1016/j.jdent.2011.1009.1005. Epub 2011 Sep 1017. **03**

(62) Lopez-Campos, J. L., Montes-Worboys, A., Calero, C., Marquez-Martin, E., Cejudo, P., Ortega, F., and Arellano, E. (2012) Cyclooxygenase-2 -765G>C polymorphism is associated with C-reactive protein levels in resistant smokers but not in chronic obstructive pulmonary disease patients. *Respir Physiol Neurobiol.*, *180*, 119-125. doi: 110.1016/j.resp.2011.1011.1001. Epub 2011 Nov 1019. **03**

(68) Moghbeli, N., Kirtane, A. J., Ray, K. K., Murphy, S. A., Gibson, C. M., Braunwald, E., and Cannon, C. P. (2005) C-reactive protein and cardiovascular outcomes in smokers versus nonsmokers in non-ST-elevation acute coronary syndrome (from the TACTICS-TIMI 18 trial). *Am J Cardiol.*, *96*, 635-638. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(77) van Dijk, W. D., Akkermans, R., Heijdra, Y., Weel, C., Schermer, T. R., Scheepers, P. T., and Lenders, J. W. (2013) The acute effect of cigarette smoking on the high-sensitivity CRP and fibrinogen biomarkers in chronic obstructive pulmonary disease patients. *Biomark Med.*, *7*, 211-219. doi: 210.2217/bmm.2212.2112. **03**

(78) van Doorn, M. B., Espirito Santo, S. M., Meijer, P., Kamerling, I. M., Schoemaker, R. C., Dirsch, V., Vollmar, A., Haffner, T., Gebhardt, R., Cohen, A. F., Princen, H. M., and Burggraaf, J. (2006) Effect of garlic powder on C-reactive protein and plasma lipids in overweight and smoking subjects. *Am J Clin Nutr.*, *84*, 1324-1329. **03**

(79) van Ree, R. M., de Vries, A. P., Oterdoom, L. H., The, T. H., Gansevoort, R. T., Homan van der Heide, J. J., van Son, W. J., Ploeg, R. J., de Jong, P. E., Gans, R. O., and Bakker, S. J. (2005) Abdominal obesity and smoking are important determinants of C-reactive protein in renal transplant recipients. *Nephrol Dial Transplant.*, *20*, 2524-2531. Epub 2005 Aug 2522. **03**

(98) Seo, S. M., Baek, S. H., Jeon, H. K., Kang, S. M., Kim, D. S., Kim, W. S., Kim, H. S., Rha, S. W., Park, J. S., Seong, I. W., Ahn, Y. K., Yoon, J. H., and Cha, T. J. (2013) Correlations between the level of high-sensitivity C-reactive protein and cardiovascular risk factors in Korean adults with cardiovascular disease or diabetes mellitus: the CALLISTO study. *J Atheroscler Thromb*, *20*, 616-622. Epub 2013 May 2016. **03**

(98) Seo, S. M., Baek, S. H., Jeon, H. K., Kang, S. M., Kim, D. S., Kim, W. S., Kim, H. S., Rha, S. W., Park, J. S., Seong, I. W., Ahn, Y. K., Yoon, J. H., and Cha, T. J. (2013) Correlations between the level of high-sensitivity C-reactive protein and cardiovascular risk factors in Korean adults with cardiovascular disease or diabetes mellitus: the CALLISTO study. *J Atheroscler Thromb*, *20*, 616-622. Epub 2013 May 2016. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(100) Vepsalainen, T., Soinio, M., Marniemi, J., Lehto, S., Juutilainen, A., Laakso, M., and Ronnemaa, T. (2011) Physical activity, high-sensitivity C-reactive protein, and total and cardiovascular disease mortality in type 2 diabetes. *Diabetes Care.*, *34*, 1492-1496. doi: 1410.2337/dc1411-0469. Epub 2011 May 1420. **03**

(101) von Kanel, R., Mills, P. J., Mausbach, B. T., Dimsdale, J. E., Patterson, T. L., Ziegler, M. G., Ancoli-Israel, S., Allison, M., Chattillion, E. A., and Grant, I. (2012) Effect of Alzheimer caregiving on circulating levels of C-reactive protein and other biomarkers relevant to cardiovascular disease risk: a longitudinal study. *Gerontology*, *58*, 354-365. doi: 310.1159/000334219. Epub 000332011 Nov 000334229. **03**

(116) Morales, E., Guerra, S., Garcia-Esteban, R., Guxens, M., Alvarez-Pedrerol, M., Bustamante, M., Estivill, X., Anto, J. M., and Sunyer, J. (2011) Maternal C-reactive protein levels in pregnancy are associated with wheezing and lower respiratory tract infections in the offspring. *Am J Obstet Gynecol.*, *204*, 164.e161-169. doi: 110.1016/j.ajog.2010.1008.1056. Epub 2010 Oct 1025. **03**

(117) Naidoo, T., Konkol, K., Biccard, B., Dudose, K., and McKune, A. J. (2012) Elevated salivary C-reactive protein predicted by low cardio-respiratory fitness and being overweight in African children. *Cardiovasc J Afr.*, *23*, 501-506. doi: 510.5830/CVJA-2012-5058. **03**

(118) Ozsu, S., Yilmaz, G., Yilmaz, I., Oztuna, F., Bulbul, Y., and Ozlu, T. (2011) C-reactive protein alone or combined with cardiac troponin T for risk stratification of respiratory intensive care unit patients. *Respir Care.*, *56*, 1002-1008. doi: 1010.4187/respcare.01007. Epub 02011 Feb 01021. **03**

(120) Sonnenschein-van der Voort, A. M., Jaddoe, V. W., Moll, H. A., Hofman, A., van der Valk, R. J., de Jongste, J. C., and Duijts, L. (2013) Influence of maternal and cord blood C-reactive protein on childhood respiratory symptoms and eczema. *Pediatr Allergy Immunol.*, *24*, 469-475. doi: 410.1111/pai.12094. Epub 12013 Jun 12016. **03**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(41) Alshaarawy, O., and Anthony, J. C. (2015) Cannabis smoking and serum C-reactive protein: a quantile regressions approach based on NHANES 2005-2010. *Drug Alcohol Depend.*, *147*:*203-7.*, 10.1016/j.drugalcdep.2014.1011.1017. Epub 2014 Nov 1028. **04**

(60) Krintus, M., Sypniewska, G., and Kuligowska-Prusinska, M. (2010) Effect of second and third generation oral contraceptives on C-reactive protein, lipids and apolipoproteins in young, non-obese, non-smoking apparently healthy women. *Clin Biochem.*, *43*, 626-628. doi: 610.1016/j.clinbiochem.2009.1012.1013. Epub 2009 Dec 1021. **04**

(83) Corsetti, J. P., Bakker, S. J., Sparks, C. E., and Dullaart, R. P. (2012) Apolipoprotein A-II influences apolipoprotein E-linked cardiovascular disease risk in women with high levels of HDL cholesterol and C-reactive protein. *PLoS One*, *7*, e39110. doi: 39110.31371/journal.pone.0039110. Epub 0032012 Jun 0039118. **04**

(84) Corsetti, J. P., Gansevoort, R. T., Bakker, S. J., Navis, G., Sparks, C. E., and Dullaart, R. P. (2012) Apolipoprotein E predicts incident cardiovascular disease risk in women but not in men with concurrently high levels of high-density lipoprotein cholesterol and C-reactive protein. *Metabolism.*, *61*, 996-1002. doi: 1010.1016/j.metabol.2011.1011.1010. Epub 2012 Jan 1005. **04**

(85) Corsetti, J. P., Gansevoort, R. T., Navis, G., Sparks, C. E., and Dullaart, R. P. (2011) LPL polymorphism (D9N) predicts cardiovascular disease risk directly and through interaction with CETP polymorphism (TaqIB) in women with high HDL cholesterol and CRP. *Atherosclerosis.*, *214*, 373-376. doi: 310.1016/j.atherosclerosis.2010.1011.1029. Epub 2010 Nov 1026. **04**

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

(88) Jeppesen, J., and Asferg, C. (2010) C-reactive protein and cardiovascular disease: differences between humans and mice. *Hypertension.*, *56*, e15; author reply e16. doi: 10.1161/HYPERTENSIONAHA.1110.155077. Epub 152010 May 155017. **05**

(109) Fazli, M., O'Connell, A., Nilsson, M., Niehaus, K., Dow, J. M., Givskov, M., Ryan, R. P., and Tolker-Nielsen, T. (2011) The CRP/FNR family protein Bcam1349 is a c-di-GMP effector that regulates biofilm formation in the respiratory pathogen Burkholderia cenocepacia. *Mol Microbiol.*, *82*, 327-341. doi: 310.1111/j.1365-2958.2011.07814.x. Epub 02011 Sep 07817. **05**

(113) Ling, M. R., Chapple, I. L., Creese, A. J., and Matthews, J. B. (2014) Effects of C-reactive protein on the neutrophil respiratory burst in vitro. *Innate Immun.*, *20*, 339-349. doi: 310.1177/1753425913493199. Epub 1753425913492013 Jul 1753425913493199. **05**

(121) Xu, P. C., Hao, J., Yang, X. W., Chang, D. Y., Chen, M., and Zhao, M. H. (2012) C-reactive protein enhances the respiratory burst of neutrophils-induced by antineutrophil cytoplasmic antibody. *Mol Immunol.*, *52*, 148-154. doi: 110.1016/j.molimm.2012.1005.1012. Epub 2012 Jun 1017. **05**

1. Kao PC, Shiesh SC, Wu TJ. Serum C-reactive protein as a marker for wellness assessment. Ann Clin Lab Sci. 2006;36(2):163-9.
2. Tillett WS, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. The Journal of experimental medicine. 1930;52(4):561-71.
3. Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clin Invest. 1993;91(4):1351-7.
4. Ridker PM, Silvertown JD. Inflammation, C-reactive protein, and atherothrombosis. J Periodontol. 2008;79(8 Suppl):1544-51. doi: 10.902/jop.2008.080249.
5. Tonstad S, Cowan JL. C-reactive protein as a predictor of disease in smokers and former smokers: a review. Int J Clin Pract. 2009;63(11):1634-41.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

6. Shah T, Newcombe P, Smeeth L, Addo J, Casas JP, Whittaker J, et al. Ancestry as a determinant of mean population C-reactive protein values: implications for cardiovascular risk prediction. Circ Cardiovasc Genet. 2010;3(5):436-44. doi: 10.1161/CIRCGENETICS.110.957431. Epub 2010 Sep 28.

7. Yamada S, Gotoh T, Nakashima Y, Kayaba K, Ishikawa S, Nago N, et al. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population : Jichi Medical School Cohort Study. Am J Epidemiol. 2001;153(12):1183-90.

8. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107(3):499-511.

9. Rackley CE. New clinical markers predictive of cardiovascular disease: the role of inflammatory mediators. Cardiol Rev. 2004;12(3):151-7.

10. Rudolf J, Lewandrowski KB. Cholesterol, lipoproteins, high-sensitivity c-reactive protein, and other risk factors for atherosclerosis. Clin Lab Med. 2014;2014 Mar;34(1):113-27.

11. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. 1999;99(2):237-42.

12. Bermudez EA, Rifai N, Buring J, Manson JE, Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler Thromb Vasc Biol. 2002;22(10):1668-73.

13. Plaisance EP, Grandjean PW. Physical activity and high-sensitivity C-reactive protein. Sports Med. 2006;36(5):443-58.

14. Nanri A, Moore MA, Kono S. Impact of C-reactive protein on disease risk and its relation to dietary factors. Asian Pac J Cancer Prev. 2007;8(2):167-77.

15. Fredrikson GN, Hedblad B, Nilsson JA, Alm R, Berglund G, Nilsson J. Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma C-reactive protein levels. Metabolism. 2004;53(11):1436-42.

16. Rodrigues IM, Klein LC. Boiled or filtered coffee? Effects of coffee and caffeine on cholesterol, fibrinogen and C-reactive protein. Toxicol Rev. 2006;25(1):55-69.

17. Corrado E, Novo S. [High sensitivity of C-reactive protein in primary prevention]. G Ital Cardiol (Rome). 2007;8(6):327-34.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

18. Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation. 2004;109(25 Suppl 1):IV6-19.

19. U.S. Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2010.

20. Life Sciences Research Office (LSRO). Biological effects assessment in the evaluation of potential reduced-risk tobacco products. Brownawell AM, editor. Bethesda, Maryland, USA2007.

21. Axelsson T, Jansson PA, Smith U, Eliasson B. Nicotine infusion acutely impairs insulin sensitivity in type 2 diabetic patients but not in healthy subjects. J Intern Med. 2001;249(6):539-44.

22. Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. PLoS Med. 2005;2(6):e160.

23. Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. J Am Coll Cardiol. 1993;22(4):1159-67.

24. Blaschke F, Bruemmer D, Yin F, Takata Y, Wang W, Fishbein MC, et al. C-reactive protein induces apoptosis in human coronary vascular smooth muscle cells. Circulation. 2004;110(5):579-87. Epub 2004 Jul 26.

25. Burke AP, Tracy RP, Kolodgie F, Malcom GT, Zieske A, Kutys R, et al. Elevated C-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies. Circulation. 2002;105(17):2019-23.

26. Chakraborti T, Mandal A, Mandal M, Das S, Chakraborti S. Complement activation in heart diseases. Role of oxidants. Cell Signal. 2000;12(9-10):607-17.

27. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350(14):1387-97.

28. Fu T, Borensztajn J. Macrophage uptake of low-density lipoprotein bound to aggregated C-reactive protein: possible mechanism of foam-cell formation in atherosclerotic lesions. Biochem J. 2002;366(Pt 1):195-201.

29. Jensen EJ, Pedersen B, Frederiksen R, Dahl R. Prospective study on the effect of smoking and nicotine substitution on leucocyte blood counts and relation between blood leucocytes and lung function. Thorax. 1998;53(9):784-9.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

30. Joseph AM, Hecht SS, Murphy SE, Carmella SG, Le CT, Zhang Y, et al. Relationships between cigarette consumption and biomarkers of tobacco toxin exposure. Cancer Epidemiol Biomarkers Prev. 2005;14(12):2963-8.

31. Joseph AM, Hecht SS, Murphy SE, Lando H, Carmella SG, Gross M, et al. Smoking reduction fails to improve clinical and biological markers of cardiac disease: a randomized controlled trial. Nicotine Tob Res. 2008;10(3):471-81.

32. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105(9):1135-43.

33. Ohsawa M, Okayama A, Nakamura M, Onoda T, Kato K, Itai K, et al. CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. Prev Med. 2005;41(2):651-6.

34. Tracy RP, Kuller LH. C-reactive protein, heart disease risk, and the popular media. Arch Intern Med. 2005;165(18):2058-60.

35. Tracy RP, Psaty BM, Macy E, Bovill EG, Cushman M, Cornell ES, et al. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. Arterioscler Thromb Vasc Biol. 1997;17(10):2167-76.

36. Tuut M, Hense HW. Smoking, other risk factors and fibrinogen levels. evidence of effect modification. Ann Epidemiol. 2001;11(4):232-8.

37. Verma S, Yeh ET. C-reactive protein and atherothrombosis--beyond a biomarker: an actual partaker of lesion formation. Am J Physiol Regul Integr Comp Physiol. 2003;285(5):R1253-6; discussion R7-8.

38. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. Eur Heart J. 2005;26(17):1765-73.

39. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. J Am Coll Cardiol. 2007;49(21):2129-38.

40. Hemingway H, Philipson P, Chen R, Fitzpatrick NK, Damant J, Shipley M, et al. Evaluating the quality of research into a single prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. PLoS Med. 2010;7(6):e1000286. doi: 10.1371/journal.pmed..

41. O'Callaghan PA, Fitzgerald A, Fogarty J, Gaffney P, Hanbidge M, Boran G, et al. New and old cardiovascular risk factors: C-reactive protein, homocysteine, cysteine and von Willebrand factor increase risk, especially in smokers. Eur J Cardiovasc Prev Rehabil. 2005;12(6):542-7.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

42. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. Am J Epidemiol. 1996;144(6):537-47.

43. Yosef-Levi IM, Grad E, Danenberg HD. [C-reactive protein and atherothrombosis--a prognostic factor or a risk factor?]. Harefuah. 2007;2007 Dec;146(12):970-4.

44. Andreeva E, Melbye H. Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. BMC Fam Pract. 2014;15:80.(doi):10.1186/471-2296-15-80.

45. Cals JW, Ament AJ, Hood K, Butler CC, Hopstaken RM, Wassink GF, et al. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. J Eval Clin Pract. 2011;17(6):1059-69. doi: 10.111/j.365-2753.010.01472.x. Epub 2010 Jul 8.

46. Cals JW, de Bock L, Beckers PJ, Francis NA, Hopstaken RM, Hood K, et al. Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. Ann Fam Med. 2013;11(2):157-64. doi: 10.1370/afm.477.

47. Engel MF, Paling FP, Hoepelman AI, van der Meer V, Oosterheert JJ. Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review. Fam Pract. 2012;29(4):383-93. doi: 10.1093/fampra/cmr119. Epub 2011 Dec 8.

48. Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. Br J Gen Pract. 2013;63(616):e787-94. doi: 10.3399/bjgp13X674477.

49. Kavanagh KE, O'Shea E, Halloran R, Cantillon P, Murphy AW. A pilot study of the use of near-patient C-Reactive Protein testing in the treatment of adult respiratory tract infections in one Irish general practice. BMC Fam Pract. 2011;12:93.(doi):10.1186/471-2296-12-93.

50. Aksu F, Capan N, Aksu K, Ofluoglu R, Canbakan S, Yavuz B, et al. C-reactive protein levels are raised in stable Chronic obstructive pulmonary disease patients independent of smoking behavior and biomass exposure. J Thorac Dis. 2013;5(4):414-21. doi: 10.3978/j.issn.2072-1439.2013.06.27.

51. Melbye H, Halvorsen DS, Hartz I, Medbo A, Brox J, Eggen AE, et al. Bronchial airflow limitation, smoking, body mass index, and statin use are strongly associated with the C-reactive protein level in the elderly. The Tromso Study 2001. Respir Med. 2007;101(12):2541-9. Epub 007 Sep 6.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

52. Pinto-Plata VM, Mullerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, et al. C-reactive protein in patients with COPD, control smokers and non-smokers. Thorax. 2006;61(1):23-8. Epub 2005 Sep 2.

53. Vaguliene N, Zemaitis M, Miliauskas S, Urboniene D, Sitkauskiene B, Sakalauskas R. Comparison of C-reactive protein levels in patients with lung cancer and chronic obstructive pulmonary disease. Medicina (Kaunas). 2011;47(8):421-7. Epub 2011 Nov 18.

54. Gimeno D, Delclos GL, Ferrie JE, De Vogli R, Elovainio M, Marmot MG, et al. Association of CRP and IL-6 with lung function in a middle-aged population initially free from self-reported respiratory problems: the Whitehall II study. Eur J Epidemiol. 2011;26(2):135-44. doi: 10.1007/s10654-010-9526-5. Epub 2011 Feb 4.

55. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Crit Rev Clin Lab Sci. 2011;48(4):155-70. doi: 10.3109/10408363.2011.599831.

56. Heikkila K, Silander K, Salomaa V, Jousilahti P, Koskinen S, Pukkala E, et al. C-reactive protein-associated genetic variants and cancer risk: findings from FINRISK 1992, FINRISK 1997 and Health 2000 studies. Eur J Cancer. 2011;47(3):404-12. doi: 10.1016/j.ejca.2010.07.032. Epub Aug 18.

57. Guo YZ, Pan L, Du CJ, Ren DQ, Xie XM. Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. Asian Pac J Cancer Prev. 2013;14(1):243-8.

58. Ko YJ, Kwon YM, Kim KH, Choi HC, Chun SH, Yoon HJ, et al. High-sensitivity C-reactive protein levels and cancer mortality. Cancer Epidemiol Biomarkers Prev. 2012;21(11):2076-86. doi: 10.1158/055-9965.EPI-12-0611.

59. Sin DD, Man SF, McWilliams A, Lam S. Progression of airway dysplasia and C-reactive protein in smokers at high risk of lung cancer. Am J Respir Crit Care Med. 2006;173(5):535-9. Epub 2005 Dec 9.

60. Alifano M, Falcoz PE, Seegers V, Roche N, Schussler O, Younes M, et al. Preresection serum C-reactive protein measurement and survival among patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg. 2011;142(5):1161-7. doi: 10.016/j.jtcvs.2011.07.021. Epub Aug 26.

61. Hong S, Kang YA, Cho BC, Kim DJ. Elevated serum C-reactive protein as a prognostic marker in small cell lung cancer. Yonsei Med J. 2012;53(1):111-7. doi: 10.3349/ymj.2012.53.1.111.

62. Kanoh Y, Abe T, Masuda N, Akahoshi T. Progression of non-small cell lung cancer: diagnostic and prognostic utility of matrix metalloproteinase-2, C-reactive protein and serum amyloid A. Oncol Rep. 2013;29(2):469-73. doi: 10.3892/or.2012.123. Epub Nov 5.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

63. Allin KH, Bojesen SE, Johansen JS, Nordestgaard BG. Cancer risk by combined levels of YKL-40 and C-reactive protein in the general population. Br J Cancer. 2012;106(1):199-205. doi: 10.1038/bjc.2011.501. Epub Nov 17.

64. Pine SR, Mechanic LE, Enewold L, Chaturvedi AK, Katki HA, Zheng YL, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. J Natl Cancer Inst. 2011;103(14):1112-22. doi: 10.093/jnci/djr216. Epub 2011 Jun 17.

65. Zhou B, Liu J, Wang ZM, Xi T. C-reactive protein, interleukin 6 and lung cancer risk: a meta-analysis. PLoS ONE. 2012;7(8):e43075. doi: 10.1371/journal.pone.0043075. Epub 2012 Aug 17.

66. Lukaszewicz-Zajac M, Mroczko B, Szmitkowski M. [The role of interleukin-6 and C-reactive protein in gastric cancer]. Pol Merkur Lekarski. 2010;29(174):382-6.

67. Douglas JB, Silverman DT, Weinstein SJ, Graubard BI, Pollak MN, Tao Y, et al. Serum C-reactive protein and risk of pancreatic cancer in two nested, case-control studies. Cancer Epidemiol Biomarkers Prev. 2011;20(2):359-69. doi: 10.1158/055-9965.EPI-10-1024. Epub 2010 Dec 20.

68. Kruse AL, Luebbers HT, Gratz KW. C-reactive protein levels: a prognostic marker for patients with head and neck cancer? Head Neck Oncol. 2010;2:21.(doi):10.1186/758-3284-2-21.

69. Hanyu O, Yoshida J, Abe E, Hirayama S, Miyake K, Aizawa Y, et al. High-sensitivity CRP reflects insulin resistance in smokers. J Atheroscler Thromb. 2009;16(5):560-7. Epub 2009 Sep 14.

70. Madsen C, Nafstad P, Eikvar L, Schwarze PE, Ronningen KS, Haaheim LL. Association between tobacco smoke exposure and levels of C-reactive protein in the Oslo II Study. Eur J Epidemiol. 2007;22(5):311-7.

71. Ahonen TM, Kautiainen HJ, Keinanen-Kiukaanniemi SM, Kumpusalo EA, Vanhala MJ. Gender difference among smoking, adiponectin, and high-sensitivity C-reactive protein. Am J Prev Med. 2008;35(6):598-601.

72. Kleber ME, Siekmeier R, Delgado G, Grammer TB, Winkelmann BR, Scharnagl H, et al. C-reactive protein and lipoprotein-associated phospholipase A2 in smokers and nonsmokers of the ludwigshafen risk and cardiovascular health study. Adv Exp Med Biol. 2015;832:15-23.

73. Mao J, Liu J, Pang X, Li M, Song J, Han C, et al. Nicotine induces the expression of C-reactive protein via MAPK-dependent signal pathway in U937 macrophages. Mol Cells. 2012;34(5):457-61. doi: 10.1007/s10059-012-0205-0. Epub 2012 Nov 6.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

74. Ohsawa M, Itai K, Onoda T, Tanno K, Sasaki S, Nakamura M, et al. Dietary intake of n-3 polyunsaturated fatty acids is inversely associated with CRP levels, especially among male smokers. Atherosclerosis. 2008;201(1):184-91. doi: 10.1016/j.atherosclerosis.2008.01.008. Epub Mar 17.

75. Frohlich M, Sund M, Lowel H, Imhof A, Hoffmeister A, Koenig W. Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). Eur Heart J. 2003;24(14):1365-72.

76. Helmersson J, Larsson A, Vessby B, Basu S. Active smoking and a history of smoking are associated with enhanced prostaglandin F(2alpha), interleukin-6 and F2-isoprostane formation in elderly men. Atherosclerosis. 2005;181(1):201-7. Epub 2005 Apr 26.

77. Lowe GD, Yarnell JW, Rumley A, Bainton D, Sweetnam PM. C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis? Arterioscler Thromb Vasc Biol. 2001;21(4):603-10.

78. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. Ann Intern Med. 2003;138(11):891-7.

79. Panagiotakos DB, Pitsavos C, Chrysohoou C, Skoumas J, Masoura C, Toutouzas P, et al. Effect of exposure to secondhand smoke on markers of inflammation: the ATTICA study. Am J Med. 2004;116(3):145-50.

80. Garcia-Lorda P, Bullo M, Balanza R, Salas-Salvado J. C-reactive protein, adiposity and cardiovascular risk factors in a Mediterranean population. Int J Obes (Lond). 2006;30(3):468-74.

81. Dietrich T, Garcia RI, de Pablo P, Schulze PC, Hoffmann K. The effects of cigarette smoking on C-reactive protein concentrations in men and women and its modification by exogenous oral hormones in women. Eur J Cardiovasc Prev Rehabil. 2007;14(5):694-700.

82. Saijo Y, Yoshioka E, Fukui T, Kawaharada M, Sata F, Sato H, et al. Effects of the Interaction between Interleukin-6 -634C/G Polymorphism and Smoking on Serum C-Reactive Protein Concentrations. Hypertens Res. 2007;30(7):593-9.

83. Levitzky YS, Guo CY, Rong J, Larson MG, Walter RE, Keaney JF, Jr., et al. Relation of smoking status to a panel of inflammatory markers: the framingham offspring. Atherosclerosis. 2008;201(1):217-24.

84. Hastie CE, Haw S, Pell JP. Impact of smoking cessation and lifetime exposure on C-reactive protein. NicotineTobRes. 2008;10(4):637-42.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

85. O'Loughlin J, Lambert M, Karp I, McGrath J, Gray-Donald K, Barnett TA, et al. Association between cigarette smoking and C-reactive protein in a representative, population-based sample of adolescents. Nicotine Tob Res. 2008;10(3):525-32. doi: 10.1080/14622200801901997.

86. Calapai G, Caputi AP, Mannucci C, Gregg EO, Pieratti A, Aurora Russo G, et al. A cross-sectional investigation of biomarkers of risk after a decade of smoking. Inhal Toxicol. 2009;21(13):1138-43.

87. Azar R, Richard A. Elevated salivary C-reactive protein levels are associated with active and passive smoking in healthy youth: A pilot study. J Inflamm (Lond). 2011;8(1):37.

88. Frost-Pineda K, Liang Q, Liu J, Rimmer L, Jin Y, Feng S, et al. Biomarkers of potential harm among adult smokers and nonsmokers in the total exposure study. Nicotine Tob Res. 2011.

89. Le-Ha C, Beilin LJ, Burrows S, Oddy WH, Hands B, Mori TA. Gender and the active smoking and high-sensitivity C-reactive protein relation in late adolescence. J Lipid Res. 2014;55(4):758-64. doi: 10.1194/jlr.P045369. Epub 2014 Feb 27.

90. Khand F, Shaikh SS, Ata MA, Shaikh SS. Evaluation of the effect of smoking on complete blood counts, serum C-reactive protein and magnesium levels in healthy adult male smokers. J Pak Med Assoc. 2015;65(1):59-61.

91. Kawada T. Relationships between the smoking status and plasma fibrinogen, white blood cell count and serum C-reactive protein in Japanese workers. Diabetes Metab Syndr. 2015;6(15):00023-5.

92. Kiechl S, Werner P, Egger G, Oberhollenzer F, Mayr M, Xu Q, et al. Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis: prospective results from the Bruneck Study. Stroke. 2002;33(9):2170-6.

93. Merghani TH, Saeed A, Alawad A. Changes in plasma IL4, TNFa and CRP in response to regular passive smoking at home among healthy school children in Khartoum, Sudan. Afr Health Sci. 2012;12(1):41-7.

94. Alyan O, Kacmaz F, Ozdemir O, Karahan Z, Taskesen T, Iyem H, et al. [High levels of high-sensitivity C-reactive protein and impaired autonomic activity in smokers]. Turk Kardiyol Dern Ars. 2008;36(6):368-75.

95. Feng D, Liu T, Wang H, Karp E, Ling W, Chen WQ. Mediation role of C-reactive protein on the association between smoking quantity and type 2 diabetes in current Chinese smokers. J Diabetes Res. 2014;2014:171538.(doi):10.1155/2014/171538. Epub 2014 Jul 3.

96. Crook MA, Scott DA, Stapleton JA, Palmer RM, Wilson RF, Sutherland G. Circulating concentrations of C-reactive protein and total sialic acid in tobacco smokers remain unchanged following one year of validated smoking cessation. Eur J Clin Invest. 2000;30(10):861-5.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

97. Rohde LE, Hennekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. Am J Cardiol. 1999;84(9):1018-22.

98. Martin de Diego CE, Gomez de Terreros Sanchez FJ, Caro de Miguel MC, Medina Font J, Matesanz Ruiz C, Gomez de Terreros Caro J. [C-reactive protein value related to a smoking history and composition of nicotine and tobacco tar]. An Med Interna. 2006;23(1):3-10.

99. Roethig HJ, Feng S, Liang Q, Liu J, Rees WA, Zedler BK. A 12-month, randomized, controlled study to evaluate exposure and cardiovascular risk factors in adult smokers switching from conventional cigarettes to a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 2008;48(5):580-91.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.