11 November 2020

N-nitrosamine Impurities in Biological Medicinal Products

Executive Summary

Taking the biological active substance, manufacture, excipients and packaging into consideration, it can be concluded that although vulnerable amines are present in biological medicinal products, there is generally expected to be no meaningful exposure to nitrosating agents. It is the position of the EFPIA member companies that it is appropriate to apply a science-based, holistic approach to evaluating the risk nitrosamine impurities presented to biological medicinal products. Therefore, for the majority of biological products there is negligible risk from nitrosamine impurities, and confirmatory testing under EMA Article 5(3) should not be required.

Introduction

Using the procedure of Article 5(3), the CHMP has finalised its opinion on the evaluation of the risk presented by N-nitrosamine impurities in human medicines (EMA/341963/2020) to now include all biological medicinal products within scope [1]. This EFPIA position considers the risk of nitrosamine impurities, as well as the impact of Article 5(3), on biological medicinal products being manufactured and developed in the biopharmaceutical industry. The risk of N-nitrosamine impurities being introduced into biological products is discussed in four parts:

1) active substance
2) chemically modified active biological substances
3) excipients (including water)
4) primary and secondary packaging/labelling

The term 'biological medicinal products' is understood in accordance with Directive 2001/83/EC as a product containing a biological substance as the active component, where (with noted exceptions e.g. certain antibiotics) a biological substance is extracted from a biological source. Therefore, the scope of the biologic medicinal products discussed in this position includes vaccines, Advanced Therapeutic Medicinal Products (ATMPs) and recombinant therapeutic proteins. The EFPIA member companies understand that a Step 1 risk assessment is now required to be performed on all classes of biological medicinal products, with Step 2 (confirmatory testing) and Step 3 (Updating of Marketing Authorisations) activities completed where a potentially significant risk is identified. This document outlines a holistic, science-based approach to the considerations for a risk

assessment of biological products. The discussion should be understood as applicable to all classes of biological medicinal product within the scope, unless otherwise described.
The overall conclusion, which aligns with that of the EMA-BWP, is that most biological medicinal products present no risk of nitrosamine impurities.
A workflow is provided (Annex 1) to assist Marketing Authorisation holders in completing a risk assessment for their biological medicinal products according to the key principles described in the following sections.

1. Active Substance

The active substances of biological medicinal products typically consist of proteins, virus particles or cells. Generally, when not subject to chemical derivatisation, such active substances do not contribute nitrosamine risk factors to the finished product and can be considered of negligible risk due to the following general considerations:

a) Biological active substances are manufactured and formulated into (including the cleaning of primary packaging components) and stored in Water for Injection (WFI),
b) Most manufacturing steps for biological active substances (and products) are sub-optimal for nitrosation reactions (time, temperature, pH, nitrosating agent concentration)
c) Liquid biological medicinal products are long-term stored under low temperature conditions that would reduce the likelihood of nitrosation which is temperature dependent.
d) Low mass, small molecule impurities are inherently cleared in the manufacturing process by standard unit operations such as bind/elute and size exclusion chromatography, and ultrafiltration/diafiltration that all purge low molecular mass impurities.
e) Biological active substances are structurally complex and highly likely to contain 'N-nitrosating agent scavenging' reactive groups (e.g. lysyl, cysteinyl),
f) Biological active substances are typically too large for cellular metabolism/activation via cytochrome P450 dependent enzymes to generate a potent mutagenic species from any nitrosamine formed from the active substance,

The following provides additional discussion on aspects of the risks of N-nitrosamine impurities, as applied to biological medicinal products:

a) The water used in manufacture and formulation is depleted in nitrosating agents.

Products for parenteral use are formulated in aqueous solution or lyophilised, for reconstitution into WFI [3] that is depleted in nitrosating agents[1]. Whereas Purified Water may be used in upstream fermentation and purification steps preceding formulation, in the manufacture of biological active substances, Purified Water is also depleted in nitrite and nitrate compared to the allowed and recorded levels in Potable Water [2]. Although Potable Water may be used in some fermentation products, no risk is presented by the nitrite content due to the clearance provided by the purification steps. Therefore, the water used in manufacture and the final WFI storage or reconstitution solvent is considered to present no meaningful risk of N-nitrosamine presence.

b) Biological medicinal products are manufactured at sub-optimal conditions for N-nitrosamine formation.

The manufacturing process is unlikely to favour nitrosation by any nitrite in water since for most process steps, the conditions are typically far from optimal for N-nitrosamine formation, with nitrosating agents only at trace impurity levels, if at all present.

The rate of nitrosation of vulnerable amines in protein or amino acids will depend upon the concentrations of the nitrite and the amine in addition to the pH, as described in the literature [2]. This reaction is optimal at or below pH 2 for low nitrite concentrations (< 1×10^{-5} M)[2] and the rate of reaction increases with increasing temperature. Although virus inactivation in biological product manufacture is typically performed at low pH (typically pH 3 to 4), the concentration of active substance is low , the duration is short (typically 1 to 3 hours) and temperature is low (typically ambient temperature less than 25 ^{o}C), compared to optimal reaction conditions. We conclude that there is no overall additional risk presented by viral inactivation due to the mitigating considerations discussed in this document: negligible levels of nitrosating agent, the presence of scavenging reactive groups, clearance

[1] Throughout this paper, reference is made to the negligible level of nitrite in the water for injection (WFI) used to manufacture and store biological medicinal products. When WFI is manufactured by distillation of Purified Water, it is expected that there would be essentially no nitrite or other known nitrosating agent present. Since the source Potable Water used to manufacture WFI can vary in nitrite/nitrate content [2], any subsequent Purified Water or WFI manufactured from Purified Water by methods other than distillation (e.g. reverse osmosis combined with ultrafiltration or deionisation), should be evaluated to assure that it too is essentially free of nitrosating agents.

[2] The concentration of nitrite in Purified Water of WFI is expected to be far below 2×10^{-7} M (approximately 0.01 mg/L) as this level is typically seen in potable water.

of small molecular mass impurities and the negligible risk presented by large nitrosated protein.

c) Biological medicinal products are stored under conditions unfavourable for temperature-dependent nitrosation reactions

Biological medicinal products are stored under conditions chosen to maintain product integrity through shelf-life to the point of administration. Therefore, most biological drug substances and products are stored frozen (drug substance) or refrigerated (drug product, 2 - 8^{o}C) and protected from light, with certain ATMP's stored as low as at -70^{o}C. The frozen storage condition greatly reduces diffusion rates for chemical reaction, when below the glass transition point for the formulated active substance or product. Any end-user ambient temperature storage or extended in-use storage such as a product pre-prepared in intravenous bags, should also be included in the evaluation.

d) Low mass small molecule impurities (from reagents, raw materials and by-products, etc) are cleared during the Manufacturing process

The manufacture of biological medicinal products involves standard processes that are proven efficient in clearing small molecules from the active substance such as orthogonal, bind/elute and size-based chromatography steps and a final ultrafiltration/diafiltration step that are designed and controlled to effectively deplete small molecular mass impurities to well below any level of concern [4]. These physical purification processes are known to be very effective. As an example, recombinant proteins expressed in biological systems undergo extensive purification involving multiple chromatography and filtration steps designed for clearance of impurities (product or process related) and are validated to clear or routinely monitored for depletion of process impurities of potential product safety concern. Due to the vast molecular mass difference between a biological active substance and the small molecular mass of potential process residual impurities, these clearance steps are typically several fold more effective at depleting small molecular mass entities than the crystallisation steps often used in API chemical syntheses to purge impurities. Similarly, large mass process impurities such as Protein A leachate or host cell protein or nucleic acid are not of concern for nitrosamine impurities since there are also effectively cleared and controlled in the manufacture of recombinant protein. Given that many biological medicinal products use several orthogonal chromatography steps with a final

ultrafiltration/diafiltration step, clearance factors of small molecular mass impurities in the order of thousands are typical.

As discussed in Gong (2018) [4] and in the EFPIA position [5], the mass difference between a small molecule impurity and the biologic active substance means that the impurities are at a much smaller proportion of administered product than would be the case for a chemically synthesised API medicinal product. This mass difference should be a consideration in assessing risk associated with dose and posology.

e) Primary amine (and thiol) groups in biological products are likely to 'mop up' nitrosating agents

Biological products contain reactive groups which behave as scavengers of nitrosating agents, e.g. primary amines, primary alpha-amides and thiols in the active substance structure or on excipients.

Polypeptides or proteins, provide a source of secondary amines potentially susceptible (e.g. tryptophanyl, histidyl, prolyl residues in polypeptide) to reaction with nitrosating agents (for example nitrites in water), though only the molecule's outer, solvent accessible amino-acid side chains would be expected to be available for any nitrosating reaction. Although it is secondary or tertiary amines that have potential to form mutagenic N-nitrosamine derivatives, primary amines and thiols may also react with nitrosating agents. However, amino acids with primary amines (lysine), or thiols (cysteine) and the protein N-terminal primary amine group (an exception being any N-terminal proline) form unstable nitrosonium intermediates that rapidly decay to the hydroxyl form and nitrogen. Therefore, primary amine (and free thiol) groups on protein or polypeptide may be considered as a scavenger of nitrosating agents [6].

f) Activation of nitroso-protein to form a potent mutagen is highly unlikely.

Large molecules with any trace N-nitrosamine, from vulnerable amine bonds in certain amino acid side groups (e.g. tryptophanyl, prolyl groups), cannot be activated to generate a potent mutagenic entity by the cellular mechanisms that activate small molecules. To form a potent mutagen – due to their stability at physiological pH - nitrosamines require metabolic activation by hydroxylation/oxidation to form an α-hydroxynitrosamine that rapidly rearranges to a diazohydroxide form that can alkylate DNA [7, and references 1 and 3, therein]. In cellular systems, this oxidation mostly occurs enzymatically by cytochrome P450 (CYP) isoenzymes. Large protein molecules, with a nitrosamine group, would be

sterically unfavourable substrates for CYP binding and activation in which the N-N bond needs to be in proximity to the haem group of CYP [8, 9]. The haem group is buried within P450 and access is only through structural channels which restricts the size of substrates. Furthermore, mutagenicity of most nitrosamines has been shown to decrease significantly as the size exceeds 12 to 14 carbons [10].

Additionally, cell compartmentalisation is a consideration since large, biologically active substances are typically, even if internalised by cells, physically separate from the genome in the cell nucleus, making any direct mutagenic activity unlikely.

Note that since current biological medicinal products are parenterally administered and not via the oral route there is no additional risk of nitrosation through gut flora nitrate/nitrite metabolism.

The totality of knowledge outlined above concludes that the risk evaluation for biological medicinal product active substances, that have not been subjected to chemical treatments such as conjugation with a synthetic entity, supports a 'negligible risk'. It is proposed that all such active substances may generally be categorised as 'no risk' of significant N-nitrosamine presence.

2. Bio-conjugated or Chemically Modified Products

Human medicinal products that contain a synthetically conjugated API component such as Antibody-Drug Conjugate (ADC) products and PEGylated bioconjugates, were already within the scope of Article 5(3). However, until recently, companies have focused their risk assessments on the synthesis of the API component relative to the dose of that entity and any possible risk presented by the conjugation reaction. Expansion of the scope for Article 5(3) requires that the biological component should also be considered, including entities of biological origin that are subsequently chemically modified and may then be used for bioconjugation. For bioconjugates, including ADC products, the nitrosamine risk evaluation may be performed for the drug-linker synthesis (drug intermediate), the recombinant protein production (drug intermediate) in addition to drug substance manufacture (conjugation of the drug intermediates followed by ultrafiltration/diafiltration to finally formulate the drug substance) and drug product manufacture (filling and closure into the primary container closure system) [5]. As outlined in Gong et al., (2018) [4], the active substance purification following bioconjugation reaction, including ultrafiltration, greatly reduces any impurity from the drug-linker synthesis expressed as a (mass ratio) percentage.

As discussed above the risk presented from a typical, chemically modified protein, protein bioconjugate or ADC is likely to be concluded as negligible unless there is a particular risk presented by the synthetic component.

3. Excipients

In general, excipients used to formulate biological medicinal products should not be assessed any differently to excipients used for products containing chemically synthesised APIs, including assessment of risk arising from the manufacture of the excipients [11]. The risks associated with impurities in sourced excipients is adequately treated in the EFPIA position on N-nitrosamines in products containing chemically synthesised APIs and is within the scope of this position for biological medicinal products.

As discussed above, in the context of biological active substances, biological products are usually stored as refrigerated liquid (in aqueous solution or suspension), 'frozen liquid' or lyophilised, formulated to give a physiologically compatible pH of the product – under conditions unfavourable for nitrosamine formation. In general, the sole source of negligible levels of nitrosating agent is from introduced impurity in the aqueous WFI solvent (see footnote 1) and potentially from the excipients. Furthermore, solid phase pharmaceutical forms, e.g. frozen or lyophilised are expected to have a greatly reduced rate of nitrosation reaction especially given the negligible levels of nitrosating agent that could conceivably be present.

Excipients used to Formulate Biological Medicinal Products

The excipients used for biological medicinal products can be different to those used to formulate chemical API products and can be required for very different purposes due to the additional complexity of biological structures and their sensitivity to the matrix of excipients and storage conditions [12]. The integrity and activity of protein and cell based products in aqueous solution, through shelf-life, would be expected to be sensitive to many factors including pH and temperature and therefore, buffering agents are typically employed along with osmolality regulators such as sucrose and stabilising excipients such as polysorbate to minimise product aggregation and effects of surface interactions. Lyophilised biologics also contain bulking agents such as mannitol.

As discussed in the API DP workflow, Guidance Note 5; Excipients at risk of forming structures of concern, specifically N-nitrosamines containing an alkyl carbon alpha to the nitrogen that contains at least one hydrogen[11, guidance note 5], should be assessed by

the appropriate company safety group with an acceptable intake (AI) for novel N-nitrosamines (i.e., those lacking toxicology data to calculate an AI) of 18 ng/day .
The excipients used for biologicals are worthy of some further reflection since certain amino acids used as excipients for biological medicinal products have amine bonds vulnerable to nitrosation e.g. histidine [13], proline [14], arginine [15]. It is also noted that a few biological medicinal products include EDTA (ethylenediaminetetraacetic acid) as a heavy metal chelator which has a reactive tertiary amine group. Any risk of nitrosamine presence through the use of EDTA should be assessed as per chemically synthesised API products but is not expected to present any additional risk to biological products when there are negligible levels of nitrosating agent.

Amino Acid Excipients

Most current, biological medicinal products are formulated using excipients that are not susceptible to nitrosation (e.g. acetate, citrate, phosphate-buffered saline) and present no risk of N-nitrosamine impurity formation *per se*. Other excipients (or adjuvants) have primary amine groups (e.g. L-glutamate, L-arginine) which can act as nitrosating agent scavengers.
Excipients or adjuvants that do contain vulnerable amine groups (e.g. L-histidine, L-proline, L-arginine) could have the potential to form N-nitrosamine impurities and, therefore, have been considered further:

L-histidine: L-histidine is a fairly common excipient in the formulation of biological medicinal products, used in low concentrations (e.g. 10 mM) as a buffering agent. While nitrosation of L-histidine is possible only one derivative, (1-nitroso-1H-imidazol-4-yl) acetohydroxamic acid (NIAH), has been shown to be mutagenic. NIAH is not in the so-called 'cohort of concern' [16] since it cannot follow the same mechanism of action with respect to mutagenicity [13] as the highly mutagenic N-nitrosamine impurities that require CYP activation and progress via a diazonium ion [17]. Furthermore, NIAH is formed by the action of multiple equivalents of nitrosating agent which under conditions of negligible nitrosating agent content (from WFI) is considered highly unlikely[3].

[3] Chemical kinetic considerations mean that it is highly unlikely that trace levels of nitrosating agent and molar excess histidine would react in multiple sequential chemical reactions to form NIAH.

L-proline: While nitrosation of the secondary amine of L-proline is possible, any nitroso-proline has been shown not to be carcinogenic as demonstrated in animal studies when L-proline and nitrite are co-ingested [18,19, 20].

L-arginine: L-arginine is a common excipient in the formulation of biological medicinal products to reduce protein aggregation and enhance thermal stability [21]. While L-arginine has no secondary or tertiary amine, nitrosation of the guanidino group of L-arginine is possible and occurs as part of endogenous cell metabolism to generate NO. However, the resulting derivative is not a nitrosamine but a nitrosourea form [22]. Studies indicate little to no carcinogenicity in animal co-fed arginine and nitrite compared to nitrite alone [23] and weakly mutagenic in an Ames test using one strain of salmonella [15]. Furthermore, the L-arginine primary amine group may also be nitrosated and hence act as a scavenger of low levels of nitrosating agent. It is concluded that the nitrosation products from L-arginine are not within the Cohort of Concern [16] and should be considered in terms of ICH M7.

4. Packaging

Primary packaging

Biological medicinal products are typically stored in impermeable glass or low permeability resin containers. These containers typically use elastomer stoppers and the risk of any ingress from the external environment is controlled through qualification of the container closure system in Container Closure Integrity studies. The contribution of any vulnerable amines from elastomer leachates to N-nitrosamine formation is also considered to be negligible due to the absence of any significant level of nitrosating agent. Current manufacture of elastomer stoppers is not known to create any nitrosating agent nor are any nitrosamines expected to leach into product, as would be detected in extractables and leachate studies.

Blisters or sachets of proteinaceous powders would require similar consideration as small molecule tablets and capsules.

The mechanism of sterilisation for packaging components should also be a consideration with particular attention to any use of nitrogen dioxide to sterilise packaging components prior to filling and assembly or as a terminal sterilisation procedure after filling and stoppering of the primary container with the medicinal product.

Secondary packaging

Biological medicinal products are packaged into primary containers such as vials, syringes or cartridges and are thereby isolated from the external environment. Although some biological medicinal products are then packaged into a blister tray and lid, secondary packaging does not present any added risk of nitrosamines reaching the product.

Conclusions

A holistic approach to the evaluation of the risk of N-nitrosamine presence in biological medicinal products is presented in this consensus position for the EFPIA member companies. Key considerations are discussed that may be employed in the risk assessments required by EMA Article 5(3) Assessment Report [1]. In summary, it is expected that, for the vast majority of biological medicinal products with no synthetically-derived component and that are not chemically-modified, there should be no risk from the active substance or its manufacturing process, and no further risks from the formulation and packing materials. Nevertheless, we cannot exclude exceptions and the conclusion of 'no risk' should be confirmed for each medicinal product on a case-by-case basis.

References

1. EMA Nitrosamine impurities in human medicinal products: Procedure under Article 5(3) of Regulation EC (No) 726/2004 – Assessment Report (EMA/369136'2020). https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf

2. Ashworth, I. W., Dirat, O., Teasdale, A. and Whiting, M. (2020) Potential for the Formation of *N*-Nitrosamines During the Manufacture of Active Pharmaceutical Ingredients: An Assessment of the Risk Posed by Trace Nitrite in Water. Organic Process Res & Dev; 24, 1629-1646.

3. Note for guidance on the quality of water for pharmaceutical use, EMA/CHMP/CVMP/QWP/496873/2018. https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-quality-water-pharmaceutical-use_en.pdf

4. Gong, H. H., Ihle, N., Jones, M. T., Kelly, K., Kott, L., Raglione, T., Whitlock, S., Zhang, M. T. and Zheng, J., (2018) Control Strategy for Small Molecule Impurities in Antibody-Drug Conjugates; AAPS PharmSciTech; DOI: 10.1208/s12249-017-0943-6

5. EFPIA position paper; CMC Regulatory Considerations for ADCs, (manuscript in preparation)

6. Kato, T. and Kikugawa, K. (1992) Proteins and amino acids as scavengers of nitrite: inhibitory effect on the formation of nitrosodimethylamine and diazoquinone. Food and Chem Tox, 30(7), 617-626.

7. Rocío López-Rodríguez, James A. McManus, Natasha S. Murphy, Martin A. Ott, and M. J. Burns (2020) Pathways for N-Nitroso Compound Formation: Secondary Amines and Beyond. Org. Process Res. Dev., 24, 1558-1585.

8. Benkaidali, L., Andre, F., Moroy, G., Tangour, B., Maurel, F. and M. Petitjean (2019) Four major channels detected in the Cytochrome P450 3A4: A step toward understanding its multispecificity. Int J Mol Sci., 20, 987-1009.

9. Urban, P., Lautier, T. Pompon, D. and G. Truan (2018) Ligand access channels in cytochrome P450 enzymes: A review. Int J Mol Sci., 19, 1617 – 1638.

10. Guttenplan, J. B. (1987) N-Nitrosamines: bacterial mutagenesis and in vitro metabolism. Mutat Res. 186; 81-134.

11. EFPIA DP workflow, - See link on EFPIA website

12. Gervasi, V., Agnol, R.D., Cullen, S., McCoy, T., Vucen, S., Crean, A. (2018) Parenteral protein formulations: An overview of approved products within the European Union. Eur J. Pharmaceutics Biophamaceutics; 131, 8 – 24.

13. Danno, G.-I., Kanazawa, K., Toda, M., Mizuno, M., Ashida, H. and Natake, M., (1993) A Mutagen from Histidine Reacted with Nitrite. J. Agric. Food Chem.; 41, 1090-1093.

14. Bolli, R., Woodtli, K., Bartschi, M., Hofferer, L., Lerch, P. (2010) L-Proline reduces IgG dimer content and enhances the stability of intravenous immunoglobulin (IVIG) solutions. Comparative Study; 38, 150 – 157.

15. Endo, H., Takahashi, K. and H. Aoyagi (1974) Screening of compounds structurally and functionally related to N-methyl-N'-nitro-N-nitrosoguanidine, a gastric carcinogen. GANN; 65, 45-54.

16. ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. (2015): EMA/CHMP/ICH /83812/2013.

17. Kushida, H., Fujita, K-I., Suzuki, A., Yamada, M., Endo, T., Nohimi, T. and Kamataki, T., (2000) Metabolic activation of N-alkylnitrosamines in genetically engineered *Salmonella typhimurium* expressing CYP2E1 or CYP2A6 together with human NADPH-cytochrome P450 reductase. Carcinogenesis; 21, 1227-1232.

18. Ohshima, H., Mahon, G. A. T., Wahrendorf, J. and Bartsch, H. (1983) Kinetic Model for Predicting Carcinogenic Effects Caused by Endogenous Nitrosation; Cancer Res.; 43, 5072-5076

19. Garcia, H. and Lijinsky, W. (1973) Studies of the tumorigenic effect in feeding of nitrosamino acids and of low doses of amines and nitrite to rats. Zeitschrift fur Krebsforschung und Klinische Onkologie; 79, 141-144.

20. Lhasa Carcinogenicity database: https://carcdb.lhasalimited.org/carcdb-frontend/

21. Ohtake, S., Kita, Y. and T. Arakawa (2011) Interactions of formulation excipients with proteins in solution and in the dried state. Adv Drug Deliv. Rev; doi:10.1016/j.addr.2011.06.011.

22. Mirvish, S. (1975) Formation of N-nitroso compounds; chemistry, kinetics, and in vivo occurrence. Tox. Appli. Pharm., 35, 325-351.

23. Hsieh, J and A. Dunn (2016) Evidence on the carcinogenicity of nitrite in combination with amines or amides. Office of Environmental Health Hazard Assessment: https://oehha.ca.gov/media/downloads/crnr/nitritehid08262016

Abbreviations

ADC	Antibody Drug Conjugate
AI	Acceptable Intake
CHMP	Committee for Medicinal Products for Human Use
ATMP	Advanced Therapy Medicinal Product
API	Active Pharmaceutical Ingredient
CYP	Cytochrome P450 enzyme family of genes
DP	Drug Product
EDTA	Ethylenediaminetetraacetic acid
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
BWP	Biologics Working Party
NIAH	(1-nitroso-1H-imidazol-4-yl) acetohydroxamic acid
WFI	Water For Injection

Contributions

The contribution of the following EFPIA MQEG Biomanufacturing, Drug Device Combination Products and MQEG CMC sub-team members to the development of this paper is acknowledged:

Andrew Lennard (Amgen)
Ian Ashworth (Astra Zeneca)
Andy Teasdale (Astra Zeneca)
Matt Popkin (GSK)
Ron Ogilvie (Pfizer)
Stuart Finnie (Astra Zeneca)
Karoline Bechtold Peters (Novartis)
Ian Mangion (Merck)
Bert Luck (Takeda)
Markus Goese (Roche)
Veit Bergendahl (Boehringer Ingelheim)
Jean-Pascal Bilgischer (UCB)
Aine Kane (Pfizer)
Schweizer, Daniel (Novartis)
Azim Celebi (Genentech)
Brad Stanley (Biogen)
Alana Arangio (Sanofi)
Philip Lienbacher (Takeda)

Lionel Randon (Merck)