

# New Generation of Highly Efficient, Long-Wavelength Photoinitiators for Dental Restoratives: From Research to Application

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Current state-of-the-art dental composites<sup>1,2</sup> are limited to layer-by-layer application due to the limited penetration depth of used blue light. Usually, the dental composite consists of about 60-80 wt% inorganic fillers and an organic matrix, comprised of photomonomers which are cured by light via the excitation of a photoinitiator (PI).<sup>3,4</sup> The most commonly used initiating system for photopolymerizable dental implants is a Type II PI consisting of camphorquinone (CQ) and ethyl 4-dimethylaminobenzoate (DMAB). However, this bimolecular PI system exhibits numerous significant drawbacks such as low reactivity and stability, especially in water-based formulations.<sup>5</sup>

The demand for an appropriate PI for visible-light curing<sup>6</sup> is high, not only for dental restoratives, but also in many other areas such as in the fields of laser-induced 3D printing and regenerative medicine. By enabling curing at wavelengths above 400 nm, the light can penetrate deeper into the composite and start a polymerization reaction because most components of the organic matrix do not absorb in this light region. Moreover, a

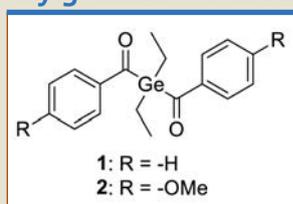
PI that photobleaches during the photopolymerization would be beneficial and also lead to an increase in curing depth.

The research toward long-wavelength PIs in our group has mainly focused on phosphorous compounds<sup>7</sup> (e.g., mono- and bisacylphosphine oxides) and germanium compounds<sup>8,9</sup> such as acylgermanes. Unfortunately, the absorption for the developed phosphor-PIs tails out at roughly 420 nm. This makes those PIs unsuitable for dental medicine since commercial LED-dental lamps are adapted to the absorption spectrum of CQ and emit in the visible-light region between about 420 and 500 nm. However, with the development of germanium-based PIs 1 and 2 (Figure 1), modern dental filling materials were improved regarding their reactivity and stability in acidic and aqueous media. Their achievable curing depth has also been greatly enhanced.

The pathway of the germanium PI from research onto a commercial product is elucidated in this paper. The general synthesis of the novel germanium PIs is described and UV-VIS absorption and photo-DSC studies of PI 1 show the absorption characteristics and photoinitiating activity under long-

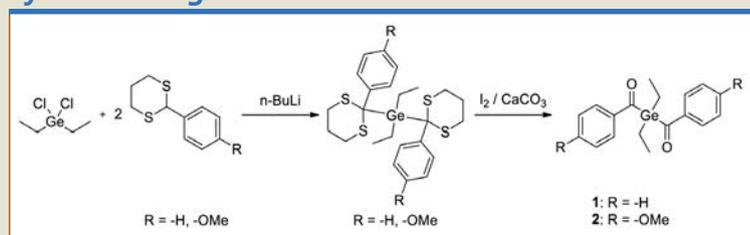
**FIGURE 1**

## Acylgermanes 1 and 2



## FIGURE 2

### Synthesis of germanium PIs 1 and 2



## Results and Discussion

### Synthesis

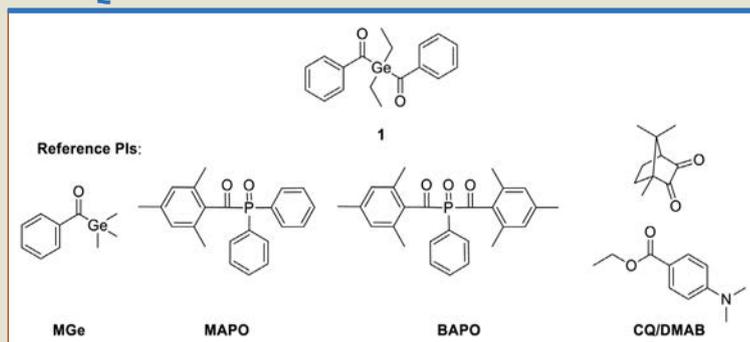
The synthesis of compounds 1 and 2 was carried out following the dithiane route<sup>13</sup> that paves the way for a wide variety of derivatives by introducing different aromatic 1,3-dithianes (Figure 2). After reacting the 1,3-dithianes with *n*-BuLi at low temperature, the corresponding carbanions are formed and react very efficiently with organic dichlorogermanium compounds (e.g., diethylgermanium dichloride) under the formation of the intermediate dithiane germanium compound. After the second reaction step, the oxidative cleavage of the protecting group with  $\text{CaCO}_3$  and Iodine, the desired PIs were isolated in satisfactory yields (1, 25%; 2, 64%).<sup>14</sup>

### UV-VIS and Photo-DSC Studies

After the successful synthesis of the germanium PIs, the first studies on absorption and photoreactivity were performed on PI 1.<sup>10</sup> UV-VIS absorption spectra of PI 1 and four reference PIs (Figure 3) were recorded in acetonitrile. It can be easily observed how acylgermanes MGe and PI 1 exhibit a red shift of the absorption

## FIGURE 3

### Germanium PI 1 and reference PIs MGe, MAPO, BAPO and CQ/DMAB

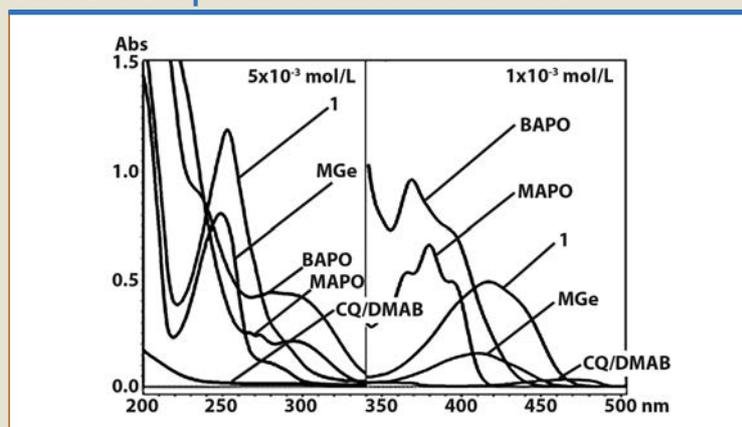


wavelength irradiation compared with phosphorous-based PIs and a Type II CQ/DMAB system.<sup>10</sup> Storage stability tests under acidic conditions were conducted and steady-state photolysis (SSP) gave an idea about quantum yields and the photobleaching effect of PI 1. The first tests on visible-light curing of dental composites showed high potential for the germanium PI 1.<sup>11</sup> Direct photophysical experiments such as time-resolved electron paramagnetic resonance spectroscopy (TR-EPR) and chemically induced dynamic nuclear polarization (CIDNP) gave insights about the mechanistic behavior of PI 1 upon irradiation.<sup>12</sup> The reactivity of germanium radicals was investigated as well and compared to benzoyl and phosphorous radicals. After the

conduction of mechanical and clinical tests, a bulk fill dental composite (Tetric EvoCeram Bulk Fill) was developed and cleared for the market.

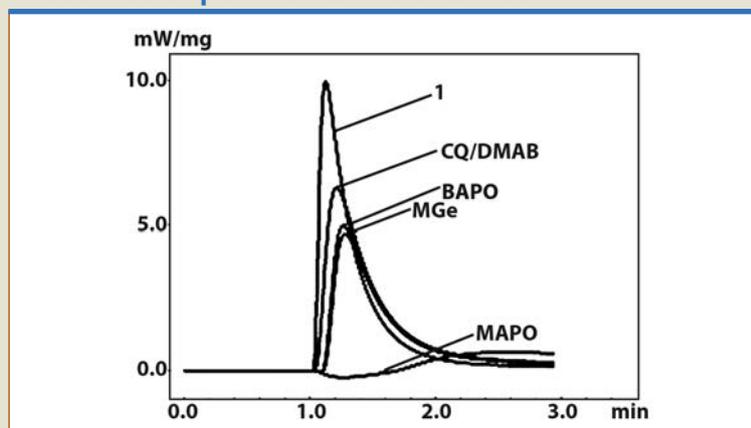
## FIGURE 4

### UV-VIS absorption of 1 and reference PIs



## FIGURE 5

### Photo-DSC experiments in dental resin



maximum of the  $n-\pi^*$  transition over 400 nm (Figure 4). The red shift of compound 1 is 20 nm and 50 nm compared to both  $n-\pi^*$  maxima of BAPO. The extinction coefficient  $\epsilon$  of 2 ( $21 \text{ L mol}^{-1} \text{ cm}^{-1}$ ) is in the same order of magnitude as  $\epsilon$  of CQ at its

absorption maximum of 468 nm ( $44 \text{ L mol}^{-1} \text{ cm}^{-1}$ ).

For the photo-DSC experiments (Figure 5),  $22 \mu\text{mol/g}$  of PI was mixed with a standard organic matrix for dental composites ( $\text{D}_3\text{MA/UDMA/Bis-GMA 1:1:1}$ ) (Figure 6). The

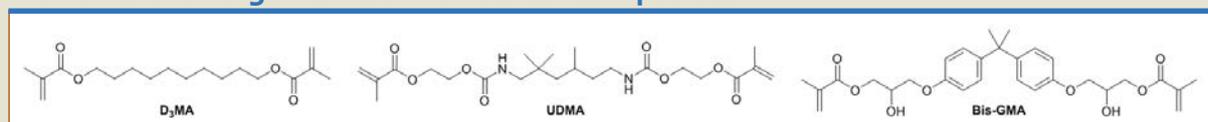
measurements were carried out under a continuous nitrogen flow with a blue LED dental lamp provided by Ivoclar Vivadent AG (Bluephase C8, 430–490 nm) and the resulting photo-DSC curves are displayed in Figure 5. As expected, the phosphorous-based PI MAPO performed very poorly under the used conditions. The germanium-based PI MGe shows similar reactivity as BAPO and the commercial CQ/DMAB PI system, but, by using the bisacylgermanium compound 1, a very good photopolymerization under visible light conditions can be achieved, even better than with the CQ/DMAB system.

### Steady-State Photolysis and Photobleaching

For the SSP, two tested PIs (1 and BAPO) were dissolved in acetonitrile to show an initial absorption of 0.5 at 365 nm. The solutions were irradiated with an LED light source (365 nm;

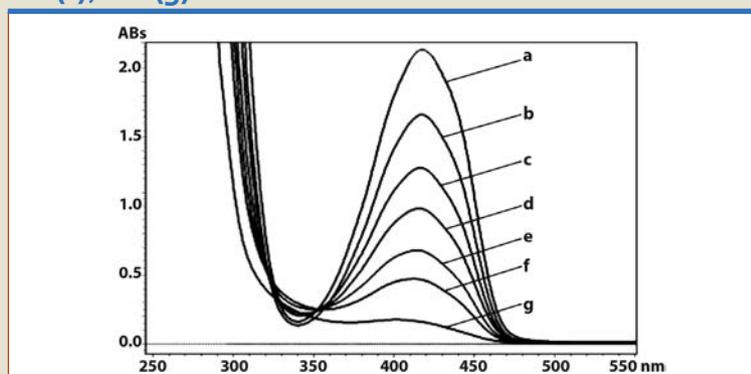
## FIGURE 6

### Monomers for organic matrix of dental composites



## FIGURE 7

### SSP of 1 after 0 h (a); 1 h (b); 2 h (c); 3 h (d); 4 h (e); 5 h (f); 6 h (g)

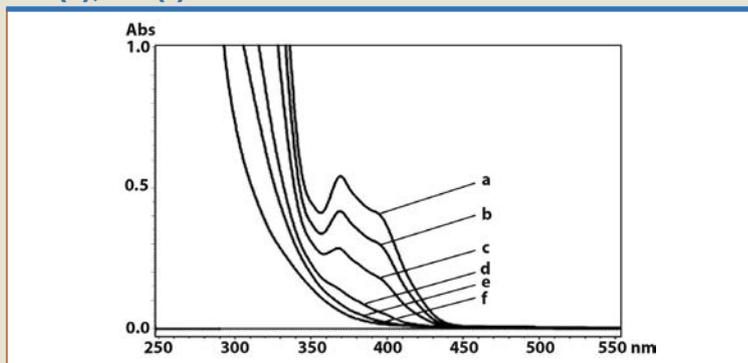


Exfo Omnicure 2000) at an intensity of  $1 \text{ W/cm}^2$ . UV-VIS measurements were conducted after set time intervals to determine the photodecomposition of the PIs (Figure 7 and Figure 8). Additionally, the photobleaching effect could be examined during those experiments since the photolysis products of PI 1 do not show absorbance in the spectral range of visible light.

The quantum yields of decomposition ( $\Phi_D$ ) were determined with the help of chemical actinometry.<sup>15</sup> The chemical actinometer used was *o*-nitrobenzaldehyde ( $\Phi_D = 0.5 \text{ mol einstein}^{-1}$ ; 310–400 nm) and an LED

## FIGURE 8

SSP of BAPO after 0 h (a); 1 h (b); 2 h (c); 3 h (d); 4 h (e); 5 h (f)



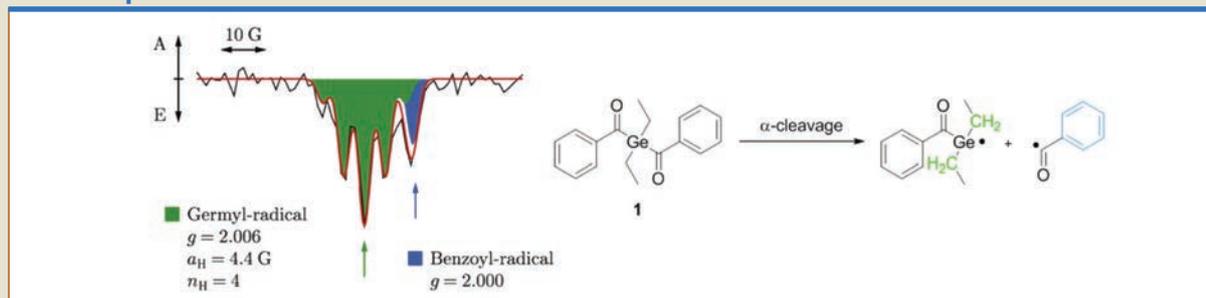
flash photolysis (Nd:YAG 355 nm) in toluene after 250 ns. Two overlapping signals for the radicals, the benzoyl-radical (blue; unresolved narrow signal;  $g = 2.000$ ) and the geryl-radical (green; quintet 1:4:6:4:1;  $g = 2.006$ ), were observed in emission (triplet mechanism).<sup>12</sup>

### <sup>1</sup>H CIDNP

The <sup>1</sup>H NMR spectrum of the PI 1 was recorded in *d*<sub>8</sub>-toluene and additionally two CIDNP spectra were measured 1 and 20 μs after the laser flash, respectively (Figure 10).<sup>12</sup> When comparing the <sup>1</sup>H NMR and CIDNP experiments, the radical recombination products (3-6) of the photolysis

## FIGURE 9

TR-EPR spectrum of PI 1



light source (365 nm) provided monochromatic irradiation.<sup>16</sup> The evaluated  $\Phi_D$  for 1 is 0.85 mol einstein<sup>-1</sup>. This shows that PI 1 is significantly more effective than BAPO with  $\Phi_D$  of 0.59 mol einstein<sup>-1</sup>.<sup>10</sup>

### Mechanistic Investigations

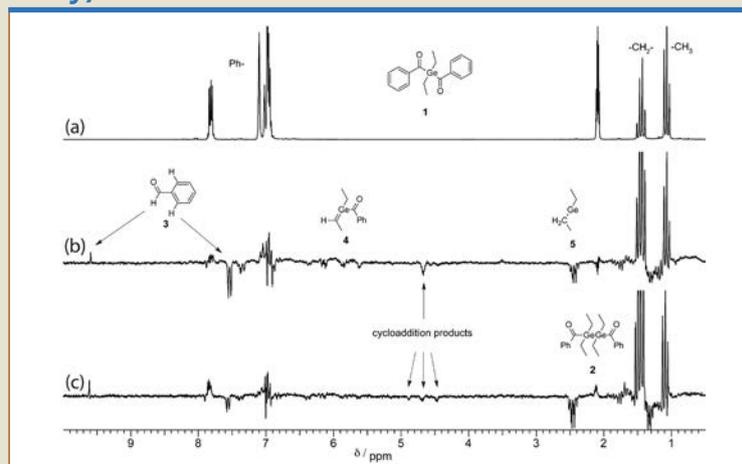
In principle, Type I PIs such as PI 1 undergo different mechanisms (e.g.,  $\alpha$ -cleavage or H-abstraction) during the initiation process that result in the formation of radicals. Those radicals can be detected by time-resolved EPR spectroscopy and their follow-up products via the <sup>1</sup>H CIDNP technique.

### Time-Resolved EPR Experiment

The measured polarized EPR spectrum of PI 1 (Figure 9) is created by laser-

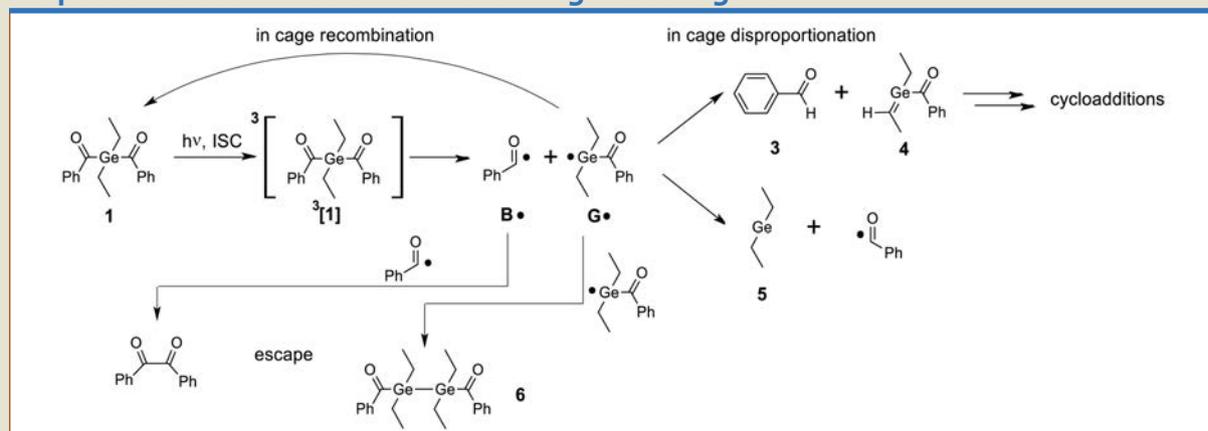
## FIGURE 10

<sup>1</sup>H NMR (a) and CIDNP spectra (1 μs (b) and 20 μs (c) delay) of 1



## FIGURE 11

### Proposed reaction mechanism following $\alpha$ -cleavage for PI 1

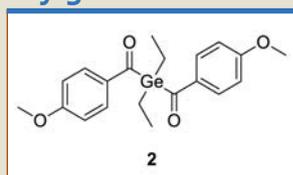


reaction of 1 can be observed and a reaction mechanism can be proposed (Figure 11).

Fast intersystem crossing (ISC) from the excited singlet to the excited triplet state<sup>3</sup> [1] is implied by the proposed mechanism and  $\alpha$ -cleavage leads to the two detected radicals, the benzoyl- and the gerymyl-radical.

## FIGURE 12

### Acylgermane 2



### Application of Germanium PI 2 in Self-Etching Adhesives and Bulk-Fill Composites

Various benzoylgermanium derivatives have been synthesized and tested as potential visible-light PIs for dental composites and compound 2 (Figure 12) was found to be the most promising candidate. This PI was therefore added to dental formulations (e.g., self-etching adhesives (SEA) and restorative composites) and tested.

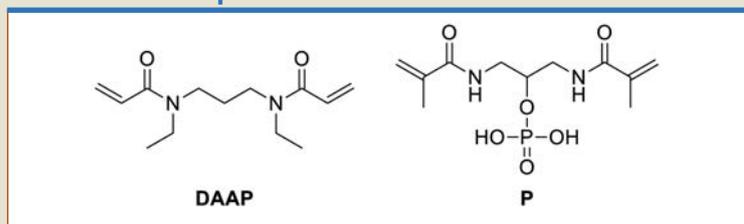
### Storage Stability of SEAs with PI 2

Current SEAs are, in principle, water-based acidic monomer formulations, here comprised of the monomers bisacrylamide (DAAP) and bismethacrylamide phosphate (P) (Figure 13). Storage stability tests have

been performed at 42°C with PIs 2 and CQ/DMAB, respectively. After defined time periods, the SEAs were cured with a halogen lamp and then the shear bond strength (SBS) on dentin was measured according to ISO/TS 11405. It is clearly shown (see Table 1) how the

## FIGURE 13

### Monomer components of tested SEA



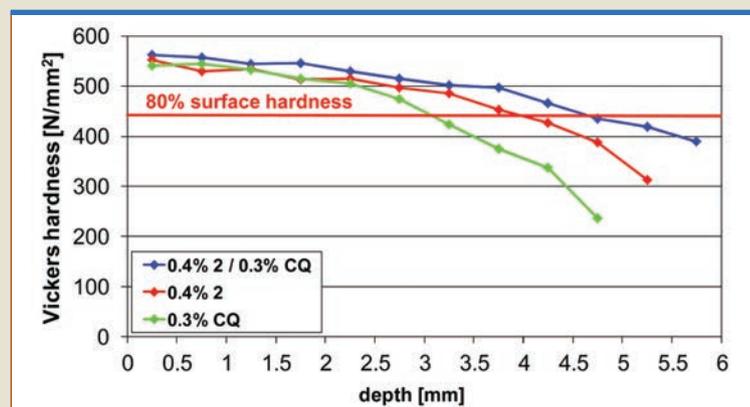
## TABLE 1

### SBS on dentin for SEAs with CQ/DMAB and 2 depending on the storage time

Formulation	SBS after 0 d [MPa]	SBS after 14 d [MPa]	SBS after 28 d [MPa]
DAAP/P with CQ/DMAB	17.0 ± 4.7	9.7 ± 3.9	-
DAAP/P with 2	28.1 ± 3.3	32.2 ± 3.2	29.2 ± 1.6

## FIGURE 14

### Vickers hardness profiles of composites with different PIs



storage stability of the SEAs has been significantly improved by replacing the acid-labile CQ/DMAB system with PI 2.

#### Increased Curing Depth of Restorative Composites with PI 2

The limited curing depth of dental composites is dependent on the composite composition (refractive index, filler load, particle size, colorant and PI), but also the photopolymerization parameters (emission spectrum of light source, intensity of light and exposure time). In order to quantify the curing depth of dental composites, Vickers hardness profiles can be recorded. Three different composites based on PI 2 and CQ/DMAB have been tested and it can be seen (Figure 14) how a composite containing a mixed initiator system of PI 2 and CQ/DMAB shows the best test results leading to an improved curing depth.

The novel PI 2 has been incorporated into a state-of-the-art dental composite material, resulting in the new bulk fill product. Compared to previous dental composites, the new bulk fill composite increases the light-curing depth from 2 mm up to 4 mm (Figure 15).

#### Toxicity

While inorganic germanium compounds are usually toxic, organic germanium compounds are often characterized by very low toxicity. The  $LD_{50}$ -value of tetraalkylgermanes ranges between 3,000 and 5,000 mg/kg, for example.<sup>17</sup> The cytotoxicity ( $XTT_{50}$ -value) of the bulk fill was investigated by means of an XTT assay. The photoinitiator was found to be non-cytotoxic.<sup>18</sup> Moreover, two mutagenicity tests were conducted.

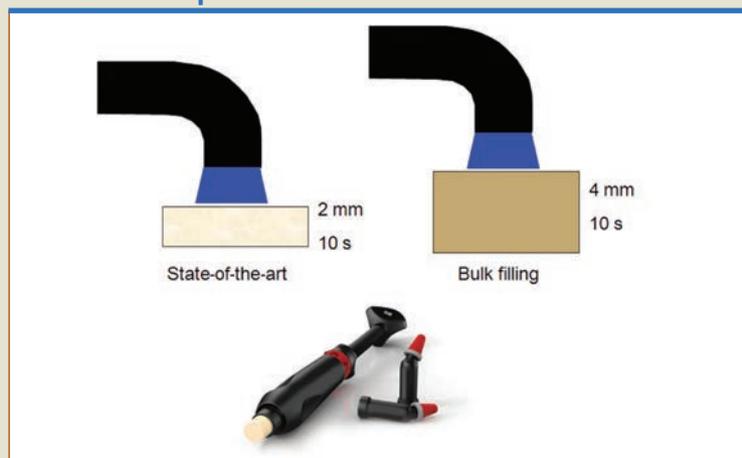
Both the Ames test (*in vitro*)<sup>19</sup> and the Mouse Micronucleus Assay (*in vivo*)<sup>20</sup> did not reveal any mutagenic effects of the bulk fill.

#### Conclusion

A new class of germanium PIs has been synthesized and investigated, leading to the commercialization of a new photoinitiator (2) in dental composites. UV-VIS absorption experiments revealed the desired bathochromic shift of the PIs (1:  $\lambda_{max} = 418.5$  nm) and photo-DSC studies proved the high photoreactivity of the acylgermanes compared to state-of-the-art PIs. Moreover, with the help of steady-state photolysis, the photobleaching effect of PIs 1 and 2 was elucidated under practical conditions enabling higher curing depths. Following those promising results for visible-light curing, time-resolved EPR and CIDNP experiments were conducted to detect the formed radicals and radical recombination products during photolysis and to propose a reaction pattern for the PIs 1 and 2. The first step of photolysis was found to be the  $\alpha$ -cleavage of the germanium-carbonyl-bond that gives a benzoyl radical and

## FIGURE 15

### New bulk fill product



a benzoyldiethylgermanium-radical. Significant follow-up products such as benzaldehyde 3 and germane 4 were found with the CIDNP technique.

The company concluded the basic studies on the germanium-based PIs and extended the study with additional mechanical and clinical tests of dental composites. As a result of the satisfying studies, the PI 2 was introduced to the market under the trade name Ivocerin® and a dental composite with improved curing depth was developed (Tetric EvoCeram Bulk Fill) using a combination of CQ/DMAB and Ivocerin® as PI system. ▶

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## References

- Moszner, N.; Salz, U.; *Macromolecular Materials and Engineering*; 2007, 292, 245-271.
- Moszner, N.; Hirt, T.; *Journal of Polymer Science Part A: Polymer Chemistry*; 2012, 50 (21), 4369-4402.
- Dietliker, K.; In Chemistry & Technology of UV & EB Formulation for Coatings, Inks & Paints Vol. 3; Photoinitiators for Free-Radical, Cationic & Anionic Polymerisation, 2nd Ed., SITA Technology Ltd., London UK; 1998.
- Fouassier, J.P.; Elsevier, *Applied Science Vol.II: Photoinitiating Systems*; 1993, 717.
- Ullrich, G.; Burtscher, P.; Salz, U.; Moszner, N.; Liska, R.; *Journal of Polymer Science Part A: Polymer Chemistry*; 2006, 44, 115-125.
- Jakubiak, J.; Rabek, J.F. *Polimery*; 1999, 44 (7/8), 447-461.
- Moszner, N.; Rheinberger, V.M.; Salz, U.; Gruber, H.; Liska, R.; Ganster, B.; Ullrich, G.; United States Patent Application Publication; 2007, U.S. 20070027229 A1 20070201.
- Moszner, N.; Salz, U.; Fischer, U.K.; Liska, R.; Gruber, H.; Ganster, B.; United States Patent Application Publication; 2008, U.S. 20080076847 A1 20080327.
- Moszner, N.; Zeuner, F.; Liska, R.; Rheinberger, V.; Lamparth, I.; Fischer, U.K.; European Patent Application; 2009, EP 2103297 A1 20090923.
- Ganster, B.; Fischer, U.K.; Moszner, N.; Liska, R.; *Macromolecules*; 2008, 41 (7); 2394-2400.
- Moszner, N.; Fischer, U.K.; Ganster, B.; Liska, R.; Rheinberger, V.; *Dental Materials*; 2008, 24 (7), 901-907.
- Neshchadin, D.; Rosspeintner, A.; Griesser, M.; Lang, B.; Mosquera-Vazquez, S.; Vauthey, E.; Gorelik, V.; Liska, R.; Hametner, C.; Ganster, B.; Saf, R.; Moszner, N.; Gescheidt, G.; *Journal of the American Chemical Society*; 2013, 135, 17314-17321.
- Brook, A.G.; Duff, J.M.; Jones, P. F.; Davis, N.R.; *Journal of the American Chemical Society*; 1967, 89, 431-434.
- Moszner, N.; Zeuner, F.; Lamparth, I.; Fischer, U.K.; *Macromolecular Materials and Engineering*; 2009, 294, 877-886.
- Kuhn, H.J.; Braslavsky, S.E.; Schmidt, R.; *Pure and Applied Chemistry*; 2004, 76 (12), 2105-2146.
- Seidl, B.; Liska, R.; Grabner, G.; *Journal of Photochemistry and Photobiology, A: Chemistry*; 2006, 180 (1/2), 109-117.
- Lukevics, E.; Ignatovich, L.; Biological activity of organogermanium compounds, In: The chemistry of organic germanium, tin and lead compounds, Z. Rappoport (Ed.), Vol. 2, John Wiley & Sons; 2002, 1653-1683.
- Heppenheimer, A; Cytotoxicity assay in vitro: Evaluation of test items in the XTT-Test with K69, RCC-CCR-Study, 1191102, 2008.
- Sokolowsky, A.; Salmonella typhimurium and Escherichia coli reverse mutation assay with K-69, RCC-CCR Study 1120104, 2007.
- Honarvar, N; Micronucleus assay in bone marrow cells of the mouse with K69, RCC-CCR-Study, 1191101, 2008.

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