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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in clinical investigation

If 'Big Pharma pay', it can keep the doctor away

A recent study suggests that doctors have less confidence in industry-funded clinical trials.

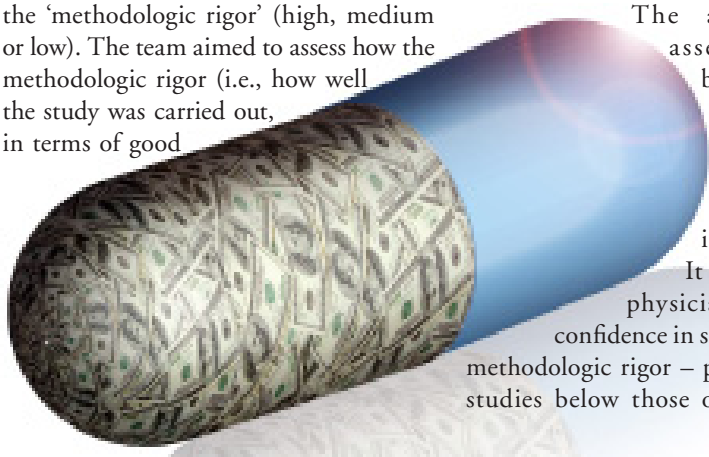
In a recently published article in the *New England Journal of Medicine*, a group of researchers present their results of a study into a potential bias against funding in clinical trials.

Speaking exclusively to *Clinical Investigation,* co-author Aaron Kesselheim, Assistant Professor of Medicine at Harvard Medical School (MA, USA), explains what lead to this research, "Financial relationships in medicine is a very controversial topic these days, and conflict of interest disclosure is the intervention taken in most circumstances to address the existence of these relationships. But few people have rigorously studied the impact of conflict of interest disclosure, and in particular its interaction with the information conveyed in the publication to which the disclosure is appended."

The team devised 27 abstracts describing "hypothetical research studies" investigating three made-up drugs against diabetes, hyperlipidemia and angina pectoris. The abstracts differed in three areas – the drug studied, the funding source (no external source, NIH- or industry-funded) and the 'methodologic rigor' (high, medium or low). The team aimed to assess how the methodologic rigor (i.e., how well the study was carried out, in terms of good clinical practice) and funding affected physicians' outlook on the drug studied.

> "...industry sponsorship negatively influences their perception of methodologic quality and reduces their willingness to believe and act on trial findings, independently of the trial's quality."

Kesselheim describes the challenge in developing these abstracts, "One challenge was figuring out how to design the hypothetical trials to display appropriately varying levels of methodological rigor. Which characteristics of clinical trial design resonate most with physicians readers? It is hard to know. Ultimately, we were fortunate for the guidance of organizations such as GRADE for setting down principles distinguishing high and low quality research. And we were heartened to see that physicians appropriately put greater faith in high-quality research and less faith in low-quality research."



The abstracts were assessed by 269 board-certified internists, who were subsequently asked numerous questions regarding the studies. It was found that physicians place more confidence in studies with higher methodologic rigor – placing 'low-rigor' studies below those of medium rigor, and 'high-rigor' studies above those of medium rigor.

Regarding financial disclosure, if the trial was industry funded – as opposed to nondisclosed funding – physicians downgraded their perceived rigor of a trial, their willingness to prescribe a drug and their confidence in the trial. This was found irrespective of the original 'methodologic rigor' of the abstract. In addition, the subjects were half as likely to prescribe drugs studied in industry- as opposed to NIH-funded trials.

The authors discuss the results of their study, describing how "industry sponsorship negatively influences their perception of methodologic quality and reduces their willingness to believe and act on trial findings, independently of the trial's quality." They suggest that this effect may negatively impact on the translation of sound clinical research into clinical practice.

Speaking about future work, Kesselheim describes that since "this study showed that disclosure is a relatively blunt tool in its effect on physician perceptions, we are interested in empirically examining other interventions intended to guide physician skepticism about funded research in addition to conflict of interest disclosure." One of the questions Kesselheim wishes to address is, "would greater data transparency help inspire appropriate reliance?"

– Written by Alice O'Hare

Source: Aaron S, Kesselheim AS, Robertson CT *et al.* A randomized study of how physicians interpret research funding disclosures. *N. Engl. J. Med.* 367, 1119–1127 (2012).

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Is the scientific purpose of pediatric cancer trials misunderstood by parents?

In a recent study published online in the *Journal of Clinical Oncology*, a group of researchers present their work into the quality of informed consent in pediatric Phase I cancer trials. The group investigated the communication between physician and parent and assessed how well the parents understood the purpose of the trial. The study revealed that many parents misunderstood this purpose, and the authors suggest that "Physician–parent communication about the purpose of Phase I research is lacking during Informed Consent Conferences (ICCs)."

Co-author Eric Kodish from the Center for Ethics, Cleveland Clinic (OH, USA) spoke to *Clinical Investigation* about what lead to this work, "As a young pediatric oncologist, I was trained to promote the idea that 'research is the standard of care' for children with cancer. As an ethicist, I was trained to question statements that appeared to have an internal contradiction or inconsistency. I became interested in research about informed consent for research in childhood cancer as an important area of scholarship to delve more deeply into the challenges and opportunities."

To carry out their study, the team directly observed 85 ICC for Phase I trials, noting how well the scientific purpose of the trial was explained. They consequently interviewed 60 parents, noting their understanding of the trial. The team described the 'scientific purpose' of a trial as "composite understanding of drug safety, dose finding, and dose escalation."

> "Physician–parent communication about the purpose of Phase I research is lacking during Informed Consent Conferences."

Their results showed that 32% of parents had "substantial understanding" of the trial, and 35% demonstrated "little or no understanding." On studying the ICC, the team found that physicians explained the goal of the trial protocol, the dose cohorts and the drug safety in 85, 43 and 23% of meetings, respectively.

Kodish describes how he would like his work translated into clinical practice: "We would be delighted if this contributed to an increased focus on the quality of informed consent. We hope for honest and compassionate discussion of the goals for a particular child and how they may or may not fit with the goals of a Phase I protocol. Specifically, we have learned that parental understanding is associated with explanation of the particular goals of a study and with explanation of the concept of dose cohorts."

Looking to future work, the team plans to continue their work into improving the quality of informed consent in childhood cancer. Kodish clarified that this is in both newly diagnosed children and those with progressive disease. He speculates that, "Training pediatric oncologists in a model of continuous quality improvement is a very logical next step."

– Written by Alice O'Hare

Source: Cousino MK, Zyzanski SJ, Yamokoski AD *et al.* Communicating and understanding the purpose of pediatric Phase I cancer trials. *J. Clin. Oncol.* doi:10.1200/JCO.2012.42.3004 (2012) (Epub ahead of print).

Results from a Phase I/II study involving an anti-IL-6R nanobody in rheumatoid arthritis patients

Ablynx (Ghent, Belgium) has announced that ALX-0061, an anti-IL-6R nanobody capable of binding to both membrane-bound and soluble IL-6, has met its efficacy end point in a Phase I/II study. The end point was reached at the end of the 12-week interim analysis of significant improvement in the key indicators of rheumatoid arthritis (RA) activity. Patients recruited had moderate-to-severe RA and a history of stable methotrexate use.

During the study, 37 RA patients were enrolled to the Phase II portion of the trial. The patients were randomized into three dose groups of intravenously administered ALX-0061 receiving either 1 mg/kg once every 4 weeks, 3 mg/kg every 4 weeks or 6 mg/kg every 8 weeks. The last randomized group received placebo. At 12 weeks the 3 mg/kg dose had achieved the most statistically significant difference in both improvement of clinical symptoms and remission in the disease activity score in an assessment of the 28 most commonly affected joints in RA when compared with placebo. All dose groups were able to show positive results in the efficacy end points, with a disease activity score of greater than 40% at week 8 and signs of onset of remission noted in some patients by week 2.

ALX-0061 was well-tolerated at all doses and its safety profile is comparable to data that has been reported for other biological disease-modifying antirheumatic drugs. At the interim analysis, there was no decrease in white blood cell counts, no cholesterol increases and no significant noted increases in liver enzymes. By week 12, 34 of the 37 participants were eligible for the determination of the efficacy end point.

Josefin-Beate Holz of Ablynx (Ghent, Belgium) commented on the outcome, "We are extremely pleased with the results from the first 12 weeks of this study. The observed high clinical remission in combination with the very encouraging safety profile demonstrates that ALX-0061 is potentially unique and differentiated compared with monoclonal antibodies that target the IL-6 pathway."

Week 24 results of the Phase I/II study are expected to be announced in the first quarter of 2013.

– Written by Priti Nagda

Source: Ablynx News and Events Press Releases; http://hugin.info/137912/R/1646263/530500.pdf

Therapeutic HPV 16/18 vaccine has promising Phase I trial results

A group from Inovio Pharmaceuticals (PA, USA) have developed a DNA-based therapeutic vaccine to combat HPV serotypes 16 and 18 infection for which, at present, only preventative vaccines exist. The researchers' recent publication in the journal *Science Translational Medicine* has reported strong immune responses to the novel VGX-3100 vaccine in Phase I trials, with Inovio CEO Joseph Kim stating that their findings could provide a breakthrough for those already infected with HPV for whom the current set of preventative vaccines are 'useless'.

HPV is the most common sexually transmitted infection and is known to cause cervical cancer, often affecting women under 40 years of age with young families. Cervical cancer is reported by the WHO as the second most common cancer in women worldwide by age-standardized incidence rate. Furthermore, in 2008, as well as 274,000 deaths occurring due to cervical cancer it was also reported that approximately 529,000 new cases of cervical cancer were reported. More than 85% of cervical cancer deaths are in developing countries. This new vaccine could allow for potential prevention of cervical dysplasia and cancer in women infected with high-risk HPV serotypes, which at present remains an unmet medical need.

> "...their findings could provide a breakthrough for those already infected with HPV for whom the current set of preventative vaccines are 'useless'"

The VGX-3100 vaccine consists of plasmid DNA with a synthetic insert encoding HPV antigens. Inovio researchers have pioneered a new platform to allow the generation of such synthetic DNA immunogens in their novel SynCon® Universal Vaccine Design system. VGX-3100 has been designed to elicit an immune response against the HPV-associated oncogenes E6 and E7, which are responsible for the transformation of HPV-infected cells into cancerous cells. The aim of the vaccine is to induce a sufficient T-cell response to destroy any infected cells. The vaccine is delivered into cells via 15 ms of electroporation to ensure the most efficient immune response.

A total of 18 patients previously treated for grade II or III cervical intraepithelial neoplasia underwent a three-dose intramuscular regimen of the VGX-3100 vaccine followed by electroporation. Immunization was observed to be well tolerated with only minor injection site reactions being reported. No dose-limiting toxicity was reported and pain assessed on a ten point visual analog scale was found to decrease from 6.2 to 1.4 after only 10 min.

A humoral immune response was found to be elicited in 100% of trial patients while analysis employing flow cytometry revealed that in 78% of patients, HPV-specific CD8+ T cells were induced and showed full functionality in the use of granzyme B and perforin to kill cells displaying HPV surface antigens. It is hoped that inducing this robust immune response will lead to the effective detection and elimination of HPV-infected cells, including those that have been altered by HPV infection into precancerous dysplasias, thus reducing the chances of cervical cancer developing.

The VGX-3100 vaccine is currently in multinational Phase II efficacy trials, which, Kim has stated, should be completed by the end of 2013. Successful development of this vaccine could lead the way not only for the treatment of other HPV-caused malignancies such as those in the head and neck but also for kidney malignancies, with the company entering into clinical trials for a similarly developed vaccine to combat WT1 in partnership with the University of Southampton (UK). With Kim claiming the company has "vaccinated over 400 patients so far using vaccines developed using our SynCon design system with no serious adverse events so far documented" the future for Inovio's missions to revolutionize vaccinations and address their current limitations looks promising.

– Written by Hannah Wilson

Sources: Bagarazzi ML, Yan J, Shen X *et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci. Transl. Med.* 4(155), 138 (2012); Inovio press release: http://ir.inovio.com/2012–10–10-Inovio-Pharmaceuticals-Cancer-Vaccine-Demonstrates-for-1st-Time-that-a-DNA-Based-Therapeutic-Vaccine-Can-Produce-Immune-Responses-to-Kill-Target-Cells; WHO: Human Papillomavirus: www.who.int/immunization/topics/hpv/en; Szarewski A. Cervarix®: a bivalent vaccine against HPV types 16 and 18, with cross-protection against other high-risk HPV types. *Expert Rev. Vaccines* 11(6), 645–657 (2012).

Presentations at EADV 2012 show ustekinumab improves quality of life in patients with plaque psoriasis

Recent presentations at the 21st European Academy of Dermatology and Venereology (EADV) congress (Prague, Czech Republic) have revealed that ustekinumab (STELARA®) can improve the long-term quality of life in patients with moderate-to-severe plaque psoriasis.

Psoriasis is an incurable, chronic, immune-mediated inflammatory disease. The combination of chronic pain and the psychological and physical burdens accompanying the disease have led to the establishment of a Europe-wide framework designed to improve the standard of care for patients. Targeted treatment selected according to the severity of the disease is key to improving quality of life.

> "The findings from these studies are promising and support a favorable benefit-to-risk profile for ustekinumab"

Results from the TRANSIT study presented at EADV 2012 showed that ustekinumab, which targets interleukin-12 and interleukin-23, significantly improved quality-of-life outcomes and was well tolerated in patients transitioning from methotrexate therapy. In addition, a presentation on the PHOENIX 2 study, involving 1230 patients with moderate-to-severe plaque psoriasis who received up to 5 years treatment with ustekinumab, showed long-term maintenance of high levels of clinical responses when being treated with ustekinumab. Furthermore, preliminary findings from the PSOLAR study revealed that, to date, no new malignancy, infection or major adverse cardiovascular events have been identified in patients undergoing ustekinumab therapy.

> "...results demonstrated in clinical trials are consistent with the real-world experience to date."

Jörg Prinz, Professor of Dermatology at the University of Munich (Munich, Germany), stated "The findings from these studies are promising and support a favorable benefit-to-risk profile for ustekinumab with up to 5 years of treatment. Importantly results demonstrated in clinical trials are consistent with the real-world experience to date. These findings further advance our understanding of biologics, not just in terms of efficacy, safety and tolerability, but also health-related quality of life."

– Written by Sophie Breeze

Source: www.businesswire.com/portal/site/biospace/index.jsp?ndmViewId=news_view&newsId=20121003006238&newsLang=en

The US FDA has approved Abraxane® for the treatment of non-small-cell lung cancer

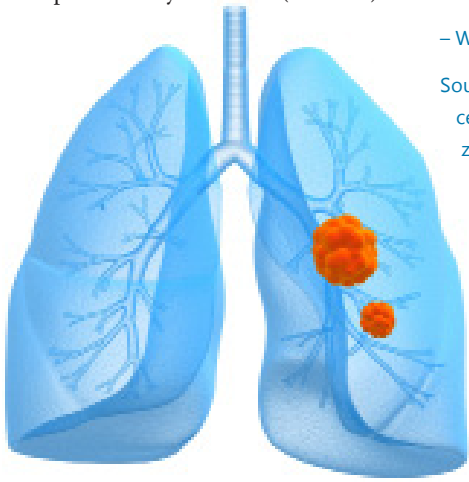
Celgene Corporation (NJ, USA) have recently announced that they have received US FDA approval for Abraxane® – a nanoparticle albumin bound paclitaxel – as a first-line treatment for non-small-cell lung cancer. It has been approved for use in combination with carboplatin in patients who are not candidates for curative surgery or radiation therapy.

> "...exciting for healthcare professionals because it offers an important new treatment option."

The approval has come following the publication of the Phase III results in the *Journal of Clinical Oncology*. In the trial 1052 patients with advanced non-small-cell lung cancer were randomized in a 1:1 fashion to receive either 100 mg/m^2 nab-paclitaxel weekly in combination with carboplatin every 3 weeks (nab-PC) or sb-paclitaxel 200 mg/m^2 every 3 weeks plus carboplatin (sb-PC). The primary end point of the trial was objective response rate.

Nab-PC demonstrated a significantly higher objective response rate than sb-PC, 33 versus 25%, respectively. It was also found that with nab-PC there was a 10% increase in progression-free survival, 6.3 versus 5.7 months, respectively and also in overall survival 12.1 versus 11.2 months, respectively.

Other improvements were also seen in neuropathy, neutropenia, arthalgia and myalgia with nab-PC. The lead author of the trial Mark Socincki (University of Pittsburgh, PA, USA) has said that the approval was "exciting for healthcare professionals because it offers an important new treatment option." The drug has already had additional regulatory submissions filed in Australia, New Zealand and Japan with results due to be announced in 2013.



– Written by Claire Attwood

Sources: Celgene Press Release: http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-newsArticle&ID=1744792&highlight; Socinski MA, Bondarenko I, Karaseva NA *et al.* Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a Phase III trial. *J. Clin. Oncol.* 30(17), 2055–2062 (2012).

Velcade® licensed in the UK for subcutaneous administration in multiple myeloma patients

Janssen (High Wycombe, UK) has announced that Velcade® (bortezomib), a proteosome inhibitor, is now licensed in the UK for subcutaneous administration for adults with multiple myeloma who meet its indications.

"The subcutaneous route of administration for bortezomib is an advance that could confer important benefits in a clinical setting"

Bortezomib has previously been administered intravenously. However, subcutaneous administration is an attractive option as it reduces the time spent in the clinic by the patient and will be beneficial for patients with, or likely to develop, peripheral neuropathy and those with poor venous access.

Approval is based upon results from a Phase III, open-label trial studying 222 bortezomib-naive relapsed multiple myeloma patients, who showed the non-inferiority of subcutaneous administrations compared with intravenous administration. Patients receiving both kinds of administration achieved a 4-cycle overall response rate of 42%. Complete response rate was 6% for those receiving subcutaneous administration, versus 8% for those receiving it intravenously. Subcutaneous bortezomib also had an improved safety profile, with patients exhibiting reduced peripheral neuropathy and Grade 3 or worse adverse events. Subcutaneous administration was also well tolerated at the injection site; 6% of patients had one or more adverse events, with 1% undergoing dose modification. All reactions are reported to have been resolved within a median of 6 days.

Graham Jackson (Freeman Hospital, Newcastle Upon Tyne, UK) commented on the approval: "The subcutaneous route of administration for bortezomib is an advance that could confer important benefits in a clinical setting. It offers the potential for reduced time in the clinic, making it more convenient for both healthcare professionals and patients alike."

– Written by Francesca Lake

Source: Janssen press release: Velcade® (bortezomib) licensed for subcutaneous administration: www.janssen.co.uk

Clinical trial to research the pneumococcal vaccine in older adults

A new clinical trial has been launched to investigate whether a higher dose of pneumococcal vaccine in adults who received an earlier generation vaccine can trigger a stronger immune response. The study is being held at six National Institute of Allergy and Infectious Disease-funded Vaccine and Treatment Evaluation Units throughout the USA and is supported by the NIH. The work looks to compare two doses of a pneumococcal vaccine approved for children aged 6 weeks to 5 years, and adults 50 years and older.

"The study may provide important new insights into the necessary immune responses needed to provide protection against pneumonia..."

According to the CDC, in 2009, pneumonia caused more than 50,000 deaths and over 1.1 million hospitalizations across the USA. Furthermore, this same year, pneumonia ranked the eighth leading cause of death in the USA with 92% of pneumonia-related deaths occurring in adults 55 years and older. The study may provide important new insights into the necessary immune responses needed to provide protection against pneumonia, which can be spread by a number of infectious agents, including viruses, bacteria and fungi.

"It is hoped that the results of this trial could help to determine the best course of action for at-risk adult populations."

The 23-valent pneumococcal polysaccharide (PPSV23) vaccine, has been the standard protection for adults over 65 from pneumococcal disease for the last 30 years. However, although this vaccine has been shown to be effective against pneumococcal meningitis and bloodstream infections, its protection against bacterial pneumococcal pneumonia is unclear. The bacteria *Streptococcus pneumoniae* causes pneumococcal pneumonia and can infect the upper respiratory tract, spreading to the lungs, blood, middle ear or nervous system. Most susceptible to this type of pneumonia are children younger than 5 years, adults older than 65 years and those that have been infected in the past. The newer 13-valent pneumococcal conjugate (PCV13) vaccine is reported to protect against bacterial pneumonia in children, however, the efficacy and effective dosage in adults has not yet been identified. In addition, previous studies have indicated that PCV13 may induce a weaker immune response in older adults who previously received the PPSV23 vaccine within the past 5 years.

The new study is being led by Lisa Jackson (Group Health Research Institute, Seattle, WA, US) and is expected to last approximately 18 months. The researchers plan to lead a Phase IIb open-label immunogenicity and safety study to evaluate dosages of PCV13 in adults previously vaccinated with PPSV23. The study will enroll 882 participants aged 55–74 years of age and investigate dosages of 0.5 and 1.0 ml of PCV13. Group I participants will consist of 294 adults who have not previously received PPSV23 and will receive an open-label dose of 0.5 ml PCV13. Group II participants will include 588 adults who have received a single dose of PPSV23 3–7 years prior to enrollment, and will be randomized to receive 0.5 ml PCV13 (Group IIA) or 1.0 ml PCV13 (Group IIB).

The study plans to demonstrate whether a 1.0 ml dose of PCV13 is significantly more immunogenic than a 0.5 ml dose among participants 55–74 years of age previously vaccinated with PPSV23. The researchers will measure immune responses using blood samples at 28 and 180 days post-injection, recording serotype-specific opsonophagocytic antibody titer and serotype specific ELISA concentration to each of the 13 vaccine serotypes. Responses will then be compared between those who had previously been vaccinated with the PPSV23 vaccine and those who had not and whether the larger dose is more immunogenic than the smaller dose amongst the previously vaccinated participants.

It is hoped that the results of this trial could help to determine the best course of action for at-risk adult populations. If the PCV13 vaccine is found to provide protection against bacterial pneumococcal pneumonia, widespread use of PCV13 could encourage the establishment of herd protection and therefore contribute to its economic viability and impact on disease.

– Written by Jenaid Rees

Sources: National Institute of Allergy and Infectious Diseases press release: www.niaid.nih.gov/news/newsreleases/2012/Pages/PneumococcalVaccine.aspx; Clinical trial page: www.clinicaltrials.gov/ct2/show/NCT01654263?term=NCT01654263&rank=1); WHO factsheet: www.who.int/mediacentre/factsheets/fs331/en; CDC webpage on pneumonia: www.cdc.gov/Features/Pneumonia/; Gladstone RA, Jefferies JM, Faust SN, Clarke SC. Pneumococcal 13-valent conjugate vaccine for the prevention of invasive pneumococcal disease in children and adults. *Expert Rev. Vaccines* 11(8), 889–902 (2012).

Antibacterial drug development to be supported by US FDA task force

The US FDA recently announced it will be supporting the development of new antibacterial drugs by forming an internal task force, the Antibacterial Drug Development Task Force, who will help in developing and revising guidance related to antibacterial drug development.

Antibiotic resistance is a worldwide issue and since development of new antibiotics is on the decline, something needs to be done. Edward Cox, director of the Office of Antimicrobial Products in FDA's Center for Drug Evaluation and Research (CDER) and co-chair of the task force explains, "The creation of this new task force comes at a critical time. Establishing new ways of developing safe and effective new antibacterial drugs is an enormous challenge and not an effort that can be accomplished alone."

> "Our hope is that this effort will result in important new breakthroughs in the field of antibacterial drug development and help in the fight against antibiotic resistance."

The task force aims to accomplish this by: determining if existing FDA guidance related to antibacterial drug development require amendments; utilizing new methods for antibacterial drug development, such as using clinical pharmacology data more broadly; and exploring innovative study designs by developing existing partnerships with think tanks.

Rachel Sherman, associate director for Medical Policy in CDER, director of CDER's Office of Medical Policy and co-chair of the task force elaborated: "By establishing this task force, FDA can help make real progress and change the paradigm. Our hope is that this effort will result in important new breakthroughs in the field of antibacterial drug development and help in the fight against antibiotic resistance."

– Written by Natasha Leeson

Source: US FDA press release: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm320643.htm

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