Healios® Research Summary

Oral Glutamine to Prevent Chemotherapy Induced Stomatitis: A Pilot Study.
Skubitz K and Anderson P, *J Lab Clin Med*, 1996; 127[2]:223-8.

- Early study tested an oral suspension of L-glutamine w/2 parts sucrose (ORA-sweet), 1 part suspending agent (ORA-plus) and 1 part water, yielding a 500mg/ml glutamine complex. Cancer patients (non-randomized) swished & swallowed' 4gm L-glutamine oral suspension twice daily (2gm amino acid/M^2/dose).

- 14 chemo-induced stomatitis adult cancer patients (8 male, 6 female): 12 receiving doxorubicin, 1 etoposide, and 1 ifosfamide, etoposide & carboplatinum. Patients started oral glutamine suspension day 1 of chemotherapy for 28 days, or for 4 days past the resolution of any post-chemotherapy mucositis.

- Maximum grade of mucositis decreased in 12 of 14 patients w/glutamine supplementation; and total number of days decreased (by ~7) in 13 patients. 13 patients self-reported mucositis was less severe w/glutamine.

Oral Glutamine Reduces the Duration and Severity of Stomatitis after Cytotoxic Cancer Chemotherapy. Anderson P, et al, *Cancer*, 1998; 83:1433-9.

- Randomized, placebo, double-blind, crossover study, tested same glutamine complex as earlier pilot study, w/sarcoma patients previously w/stomatitis, serving as their own controls over 4 courses of chemotherapy.

- 24 patients, results data available for 13 (10 pediatric, 3 adult): 12 treated w/doxorubicin-containing regimens, 1 w/high dose methotrexate. Patients swished & swallowed the glutamine (active) or glycine (placebo) twice daily, beginning on the day of chemotherapy and continuing for at least 14 days after chemotherapy.

- Glutamine supplementation during & after chemotherapy significantly reduced both the duration (4.5 days less) & severity (Grade 2 or above was 4 days less) of stomatitis, compared w/placebo.

Effect of Low-dose Oral Glutamine on Painful Stomatitis During Bone Marrow Transplantation. Anderson P, et al, *Bone Marrow Transplantation*, 1998; 22:339–344.

- First clinical (randomized, double-blind, placebo-controlled) tested same glutamine complex as earlier pilot study. BMT patients, swished & swallowed 4gm L-glutamine oral suspension 4x daily (1gm amino acid/M^2/dose).

- 193 patients stratified by transplant type (autologous, matched sibling donor or unrelated donor) and randomized to A (glutamine) or B (placebo/glycine), from admission continuing until 28 days after infusion.

- In autologous BMT patients, glutamine significantly reduced mouth pain by self-report and by opiate use, but had no effect w/matched sibling BMT. Day 28 survival of allogeneic patients was improved by glutamine.

Healios® Research Summary (continued)

AES-14 Facilitates Rapid Intracellular Transport of High Levels of L-Glutamine in Mucosal Epithelial Cells. [Abstract 2410]. Petit R, et al. *Proc Am Soc Clin Oncol*, 2000; 19:612a.

- Invitro study showed AES-14 (brand name Saforis*) proprietary glutamine-disaccharide formula administered orally, compared w/other available forms of glutamine, facilitated glutamine uptake by epithelial oral mucosal cells more than 100 times. The increase in intracellular glutamine levels occurred rapidly, within 10 seconds. *note: Saforis was Healios prior

AES-14 (uptake-enhanced L-glutamine suspension) Reduces Severe Mucositis in Acute Radiation Model where Aqueous L-Glutamine Suspension is Ineffective [Abstract 2861]. Petit R, *Shinal E. Proc Am Soc Clin Oncol*, 2002; 21:261b.

- Saforis prevented OM in a well-validated animal model of mucosal injury, and significant activity was demonstrated compared with placebo.

Phase III Study: AES-14 in Chemotherapy Patients At Risk for Mucositis. [Abstract 2917]. Peterson D, *Petit R. Proc Am Soc Clin Oncol,* 2003; 22:725.

- In cancer patients w/previous chemotherapy-related OM, Saforis glutamine-disaccharide (2.5gm L-glutamine per 5mL, 3 times daily, for a total daily dose of 7.5gm) significantly reduced the duration of OM compared with placebo.

Randomized, Placebo-Controlled Trial of Saforis for Prevention and Treatment of Oral Mucositis in Breast Cancer Patients Receiving Anthracycline-based Chemotherapy. Peterson et al, *Cancer*, 2007; 109:322–31.

- Clinical study tested efficacy and safety of oral glutamine-disaccharide suspension Saforis for reducing incidence of WHO grade 2 or above in patients receiving mucotoxic cancer therapy for breast cancer.

  (Authors note: Saforis has been studied in 4 previously reported clinical studies in various patient populations: cancer patients w/previous chemo-related OM, Saforis significantly reduced the duration of OM compared w/placebo, to reduce incidence of moderate to severe OM compared w/placebo, and to significantly reduce severity of OM compared w/previous chemotherapy cycle. [Prior studies identified in blue]

- 326 breast cancer patients w/chemo-induced mucositis of (WHO) grade 2 or above, were randomized to Saforis or placebo during treatment cycle 1 (21 days), then crossed over to alternate in cycle 2.

- Oral administration of Saforis (2.5g per 5mL, 3 times daily, for a total daily dose of 7.5gm) began on day 1 of chemo and continued for 14 days after the last dose of chemo in patients who did not develop OM or until 5 days after resolution of OM for patients who experienced OM or to the end of the treatment cycle. Patients swished for 30 seconds then swallowed.

- Compared w/placebo, Saforis significantly reduced incidence of clinically significant WHO grade 2 or above OM (38.7% vs 49.7%; P=.026)) and severe WHO grade 3 or above (1.2% vs 6.7%; P=.005) in cycle 1. Saforis also significantly reduced the worst OM Assessment Scale ulceration score in cycle 1 compared w/placebo (P=.013). Patients taking Saforis in cycle 1 had lower-than-expected OM incidence when crossed over to placebo in cycle 2, indicating a significant carryover effect (P=.027).

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