

# 6to Simposio Internacional sobre Análogos de GnRH en el Cáncer y la Reproducción Humana

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REPORTES

## Introducción

El 6to Simposio Internacional sobre Análogos de GnRH en el Cáncer y la Reproducción Humana se celebró entre el 8 y el 11 de Febrero del 2001 en Ginebra, Suiza.

En el programa científico del evento se abordaron los siguientes aspectos:

- La biología de los sistemas de GnRH en el cáncer y la reproducción humana.
- Oportunidades de Ganirelix, antagonista de GnRH, en la hiperestimulación ovárica controlada.
- Las experiencias clínicas con Cetrotide® (Cetrorelix) antagonista de GnRH.
- Reproducción asistida: controversias.
- El papel de los agonistas de GnRH y el bloqueo androgénico en el cáncer de próstata.
- Acciones ováricas de los antagonistas de GnRH.
- Análogos de GnRH en el manejo de la endometriosis.
- GnRH - su rol en el cáncer de próstata.
- Análogos de GnRH en el manejo del fibroma uterino.
- Análogos de GnRH en cáncer de ovario y mama.

En el presente reporte nos vamos a referir al empleo de análogos agonistas y antagonistas de GnRH en el tratamiento del cáncer de próstata (CP), teniendo en cuenta la importancia que reviste esta patología en la actualidad. El CP es el tumor más frecuente en el hombre en los Estados Unidos de Norteamérica (EE.UU.) y en otros países. En 1999, se diagnosticaron en EE.UU. aproximadamente 179 300 nuevos casos de CP. Por otra parte, de acuerdo al Instituto Nacional del Cáncer (NCI) el costo anual para EE.UU. por esta patología puede ser de 15 mil millones de USD.

## El papel de los agonistas de GnRH en el cáncer de próstata

El aislamiento, identificación y síntesis, en 1971, de la hormona liberadora de gonadotropinas (GnRH) u hormona liberadora de la hormona luteinizante (LHRH) marcó el inicio de las investigaciones que condujeron a la aplicación de la GnRH y sus análogos en el tratamiento de enfermedades dependientes de esteroides sexuales (cáncer de próstata, mama, ovario y endometrio hormono-dependientes), en la inhibición de la aparición de la pubertad precoz y en la inducción de la ovulación y la superovulación entre otras.

Aproximadamente el 85% de los CP recién diagnosticados son tumores hormono-dependientes que requieren de la testosterona (T) para su crecimiento y desarrollo. Por ende, en estos casos, la supresión androgénica constituye la base del tratamiento de la enfermedad. Sin embargo, los análogos agonistas de GnRH producen inicialmente un aumento indeseado de los niveles de T, fenómeno conocido como "flare-up" y que puede agravar la sintomatología del CP con aumento del dolor y posibles lesiones óseas como el aplastamiento vertebral, efecto que puede ser con-

trarrestado con la administración previa de antian-drógenos.

En el Simposio se debatieron los resultados clínicos con el empleo de implantes de análogos agonistas de GnRH de larga duración como vía para disminuir la frecuencia de las inyecciones, disminución de los costos de los tratamientos y en aras de aumentar la calidad de vida de los pacientes.

Un ejemplo lo constituyó el empleo de *Viadur*, un nuevo sistema implantable de liberación de *Leuprolide*, agonista de GnRH, el que proporcionó en pacientes con CP avanzado una supresión efectiva de T durante 12 meses (reporte "Safety and efficacy of an implantable Leuprolide delivery system in patients with advanced prostate cancer"). Por otra parte, el empleo de un simple implante de *Histrelin* (50 mg), superagonista de GnRH, fue capaz de mantener una supresión completa de LH y T por más de 3 años en pacientes con CP metastásico y después de retirado permitió una recuperación inmediata de los niveles de LH y T, efecto muy beneficioso en el caso que el paciente no tolere la deficiencia androgénica (reporte "The Histrelin implant results medical castration for over 3 years with immediate reversal of testosterone suppression on implant removal").

En los casos de CP clínicamente localizado están indicados la prostatectomía radical y la radioterapia, reservando para casos específicos la observación. Sin embargo, hoy día, con una apropiada campaña masiva de detección de CP en la población sana (*screening*), el 99% de los CP pueden ser diagnosticados en el estadio localizable y ser potencialmente curados, a partir de la utilización inmediata del bloqueo androgénico prolongado (reporte "Key role of LHRH agonist in the first pivotal studies shown to improve survival in localized prostate cancer").

El tratamiento del CP localmente avanzado con radioterapia y *Goserelina* (*Zoladex*), agonista de GnRH, mostró beneficios clínicos importantes al mejorar la supervivencia global comparado con pacientes que recibieron la radioterapia sola (reporte "A review of adjuvant luteinizing hormone releasing hormone (LHRH) agonist therapy in prostate cancer").

## El papel de los antagonistas de GnRH en el cáncer de próstata

En el Simposio se presentaron los resultados de ensayos clínicos con el empleo de antagonistas de tercera generación, capaces de suprimir rápidamente y con carácter reversible las funciones testiculares de una manera dosis dependiente. Por ejemplo, *Abarelix*, primer antagonista puro de GnRH, produjo la castración médica en aproximadamente 70% de los pacientes, en la primera semana de tratamiento, comparado con 0% en pacientes que recibieron *Leuprolide* o *Leuprolide*

más bicalutamida. Además evitó el “flare-up” en 100% de los pacientes e indujo la remisión en pacientes con CP avanzado, en los cuales los agonistas de GnRH estaban contraindicados (reporte “History of GnRH antagonists in the management of hormonally responsive disorders – a historical overview”). Por otra parte, el empleo de un implante de *Abarelix* (100 mg), en monoterapia fue capaz de inducir una reducción más rápida de PSA, LH, FSH, DHT y T comparado con agonistas de GnRH en monoterapia o en el llamado bloqueo androgénico máximo, demostrando la superioridad de los análogos antagonistas sobre los agonistas de GnRH existentes (reportes “Abarelix: clinical benefits in prostate cancer” y “Pharmacological and biochemical properties of Abarelix, a pure GnRH antagonist”). Abarelix está siendo desarrollado conjuntamente por Amgen y Praecis Pharmaceuticals en Estados Unidos de Norteamérica, Canadá y en territorios del Pacífico y por Praecis Pharmaceuticals y Sanofi-Synthelabo en Europa, México y Sudamérica (comunicación personal del Dr. Marc Garnick).

Sin embargo, durante el evento se hizo evidente que ninguno de los agonistas o antagonistas que han sido clínicamente testados fueron capaces de suprimir totalmente la LH o la FSH.

### Nuevos enfoques terapéuticos

Debemos destacar que el simposio se concentró fundamentalmente en el empleo de análogos de GnRH en el tratamiento del CP y no abundaron otras estrategias terapéuticas para tratar esta enfermedad, excepto un nuevo procedimiento inmunológico en el que se utilizó un análogo de GnRH conjugado al toxoide tetánico, el cual fue administrado a pacientes con CP metastásico en un régimen de tres inmunizaciones de 80 µg cada una. A las 12 semanas no observaron una producción consistente de anticuerpos anti-GnRH por lo que continúan realizando estudios empleando una formulación alternativa para hacer posible la administración de dosis mayores del péptido (reporte “Phase I/II clinical study of a novel GnRH analogue”).

En los participantes existió el consenso de que la deprivación de gonadotropinas y de andrógeno continua siendo una opción importante en el tratamiento del carcinoma de próstata hormono-dependiente avanzado. Sin embargo, sigue siendo improbable algún efecto curativo a largo plazo de la terapia hormonal y las complicaciones que origina, argumentan contra su uso rutinario en forma temprana en el curso de la enfermedad.

### Safety and Efficacy of an Implantable Leuprolide Delivery System in Patients with Advanced Prostate Cancer

Jackson E Fowler for the Viadur Study Group

We evaluated the pharmacokinetics, safety and efficacy of the implantable Viadur leuprolide delivery system during 12 months in patients with advanced prostatic cancer. Our open label, multicenter, dose ranging study was done in 2 phases. The treatment phase was a stratified, randomized, parallel evaluation of the safety and efficacy of 1 or 2 implants. The safety extension phase assessed the long-term safety

and efficacy of 1 implant. Implant insertion and removal, pharmacokinetic profile and patient satisfaction were also evaluated. The primary efficacy parameter was testosterone suppression for 12 months but luteinizing hormone and prostate specific antigen were also evaluated. Of the 51 patients 27 received 1 and 24 received 2 implants, of whom 49 completed the 12-month treatment phase. Steady serum leuprolide concentration was maintained from day 3 through the remainder of the 12-month treatment phase and for 2 months after reimplantation. Implantation and reimplantation were well tolerated and acceptable to physicians and patients. Testosterone suppression to the castrate range was 100% in each group. At 12 months mean prostate specific antigen decreased from a baseline of approximately 84% and 91% in groups 1 and 2, respectively. Serious adverse events in 15 patients were not attributable to treatment. The implantable leuprolide delivery system provides effective suppression of testosterone in patients with advanced prostate cancer.

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### The Histrelin Implant Results in Medical Castration for Over 3 Years With Immediate Reversal of Testosterone Suppression on Implant Removal

Spitz IM,<sup>1</sup> Lindenberg T,<sup>1</sup> Chertin B,<sup>2</sup> Gelber H,<sup>1</sup> Leiter C,<sup>1</sup> Kuzma P,<sup>3</sup> Farkas A<sup>2</sup>

Testosterone (T) suppression in patients with metastatic prostate cancer is usually achieved with long acting depot preparations of GnRH superagonists administered every one to three months. We describe the response to a hydrogel implant containing 50 mg of Histrelin. The implant was inserted subcutaneously into the arm under local anesthesia in 15 patients with metastatic prostate cancer. Two weeks prior to insertion, all patients were given antiandrogens. This was continued for up to 12 weeks after insertion. Following insertion, LH and T decreased and by 28 days LH was suppressed to below assay sensitivity (< 0.1 mIU/mL) and T was below castration levels (< 0.2 ng/mL) in all subjects. PSA levels commenced falling during antiandrogen therapy and further decreases were evident following insertion. PSA levels remained suppressed in 11 patients and increased in 4. In contrast, LH and T levels remained suppressed in all patients. The major side effects reported were decreased sexual drive and impotence. After the implants had been in place for one year, challenge tests were performed with a single bolus of GnRH (100 µg) administered at 3 monthly intervals. LH was persistently suppressed in the patients despite GnRH challenge. After a distribution phase lasting 8 weeks, circulatory histrelin levels stabilized and remained constant for the duration of the study. Implants were removed from 9 patients 35-37 months after insertion. One week later, histrelin levels were undetectable and LH and T began to increase. The residual amount of histrelin in two implants removed after 2 years was 21 mg/implant. Implants removed after 3 years showed an *in vitro* release rate of 15 µg/ week. Our results have shown

that a single histrelin implant is effective in maintaining full LH and testosterone suppression for over three years. The precise duration of its effect is unknown but based on the residual histrelin in implants following removal, it should be over 4 years. The histrelin implant is an improvement over existing preparations. During implant use, histrelin levels remain stable and there is no T escape. There was no LH response to GnRH challenge. Unlike depot GnRH preparations, where prolonged T suppression may occur, LH and T rise immediately after the implant is removed. This is useful if the patient cannot tolerate androgen deficiency.

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<sup>2</sup>Department of Urology, Shaare Zedek Medical Center, Jerusalem, Israel.

<sup>3</sup>Hydromed Sciences, Cranbury, NJ, USA.

## Key Role of LHRH Agonists in the First Pivotal Studies Shown to Improve Survival in Localized Prostate Cancer

Labrie F, Candas B, Cusan L, Gomez JL, Lévesque J, Chevrette E

Progress in the field of prostate cancer therapy has been seriously limited until recently by the absence of data showing that early treatment prolongs life. The discovery that LHRH agonists induce medical castration as efficiently as orchiectomy or surgical castration, with an absence of side effects other than those related to inhibition of testicular androgens, has permitted to perform the first prospective and randomized clinical studies using androgen blockade in localized prostate cancer. Previously, when only surgical castration and high doses of estrogens were available to block testicular androgen secretion, studies were usually not judged as being acceptable for patients with localized disease. With the discovery of medical castration, all the seven randomized studies published since 1997 have shown that treatment of localized prostate cancer or early treatment saves lives. As an example, the first prospective randomized study of screening for prostate cancer, namely the Quebec study, shows a 68% decrease in cancer-specific death at 10 years of follow-up. On the other hand, the addition of androgen blockade to radiotherapy has been shown in the four studies reported to decrease prostate cancer death by 45% at five years. In a longer-term study, Messing *et al.* have shown a 81% decrease in cancer-specific death at 9 years in patients with positive pelvic nodes who received immediate androgen blockade compared to delayed treatment. In fact, cancer-specific death at 7 years of median follow-up was observed in less than 5% of patients when continuous treatment was started early at the stage of clinically localized disease compared to 70 to 80% of deaths when treatment was started late in patients with bone metastases. Today, with appropriate screening, 99% of prostate cancers can be diagnosed at the localized and potentially curable stage. In fact, starting androgen blockade at time of diagnosis of localized disease can achieve long-term control of the disease in close to 100% of patients and even cure the disease in the majority of them, as evidenced by maintenance of undetectable PSA in 85% of patients four years after cessation of long-term combined androgen blockade.

In summary, the recently available data demonstrate that the use of regular PSA screening and immediate treatment using androgen blockage can dramatically reduce mortality in prostate cancer patients.

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## A Review of Adjuvant Luteinizing Hormone Releasing Hormone (LHRH) Agonist Therapy in Prostate Cancer

Fourcade R

Patients with prostate cancer are commonly diagnosed with localized rather than metastatic disease. However, a significant proportion of patients with localized disease still encounter disease progression often leading to death despite having radical surgery or radiotherapy. Patients treated with radiotherapy and goserelin (Zoladex™) adjuvant therapy for locally advanced prostate cancer showed improvement in estimated 5-year survival compared with patients receiving radiotherapy alone. Patients with a poor prognosis showed improvement in overall survival after long-term adjuvant treatment. Patients who underwent radical prostatectomy responded well to adjuvant goserelin therapy, with significant increases in their overall survival compared with the surgery only group. Furthermore, improved disease-free survival of prostate cancer patients has been reported with adjuvant goserelin therapy. In another study, patients receiving goserelin and flutamide, prior to radiotherapy, showed increased disease-free survival when receiving further goserelin treatment compared with those patients who did not receive follow-up adjuvant therapy. Adjuvant therapy with goserelin has important clinical benefits in patients with prostate cancer. Current evidence suggests that adjuvant LHRH agonist therapy is the preferred choice for the treatment of prostate cancer following either radiotherapy or radical prostatectomy.

Service d'Urologie, Centre Hospitalier d'Auxerre, France.

## History of GnRH Antagonists in the Management of Hormonally Responsive Disorders –a Historical Overview

Garnick MB, MD Chief Medical Officer

Ever since Dr. Andrew Schally discovered the structure of GnRH, many investigative teams have identified both agonists and antagonists of the GnRH receptor. Extensive work performed in the late 1970's and early 1980's demonstrated the utility of LHRH superagonists in a variety of medical conditions requiring the cessation of production of both male and female sex steroids. The introduction of leuprolide acetate for the management of metastatic prostate cancer, followed by goserelin acetate marked the beginning of the use of LHRH analogues in the management of prostate cancer in the United States. More recently additional sixth amino acid substitutions of native LHRH have been introduced and include triptorelin and other longer acting formulations of leuprolide. Additional clinical indica-

tions have followed with regulatory approvals, and represent the expected physiological approach induced by the action of LHRH agonist. These indications include endometriosis, uterine fibroids, and precocious puberty. Multiple other indications are currently under investigation and will likely expand in future years.

Ongoing work with GnRH antagonists did not proceed as smoothly and rapidly during this time. Based on limited water solubility, localized and systemic histamine release and difficult in formulation for long term administration, and the requirement for larger doses of antagonist to suppress the LHRH receptor (when compared to agonists), the commercialization of GnRH antagonists lagged behind their agonist counterparts. However, ongoing work clearly demonstrated the improved utility of GnRH antagonists in circumstances in which acute suppression of the hypothalamic-pituitary-gonadal axis was required.

The development of GnRH antagonists was highlighted just recently with the regulatory approval of two such peptides, cetrorelix and ganorelix, for the short term management of *in vitro* reproduction indications. The development of abarelix depot represents one of the more advanced programs in which a GnRH antagonist has been utilized for the chronic usage in the management of prostate cancer. Abarelix has been formulated into a long term depot suspension which allows every 4 week dosing. Randomized, prospective sponsor blinded studies have been conducted that has compared abarelix monotherapy to either leuprolide depot alone as monotherapy (Study 149-98-02) or abarelix depot monotherapy to the combination of leuprolide depot plus the oral administration of bicalutamide (Study 149-98-03).

Both of these studies evaluated the avoidance of testosterone surge and rapidity of achieving medical castration within the first week of treatment in prostate cancer patients requiring the benefits of initial hormonal therapy. Abarelix depot universally (100% of patients) avoided the testosterone surge, compared to avoidance of surge by either leuprolide (18%,  $p < 0,001$ ) or the combination of leuprolide plus bicalutamide (14%,  $p < 0.001$ ). In addition, approximately 70% of patients receiving abarelix were medically castrate within the first week of therapy compared to 0% of patients receiving either leuprolide or leuprolide plus bicalutamide.

In both studies, the ability to achieve and maintain castration levels of testosterone were equivalent from days 29 through day 85 of treatment. Safety evaluations were comparable between abarelix and leuprolide. More patients receiving bicalutamide withdrew because of adverse events. One surprising finding of these studies demonstrated a differential effect on follicle stimulating hormone levels. The use of abarelix caused an immediate suppression of FSH values, which were sustained. In contrast, LHRH agonists caused the expected surge, followed by a nadir, and then a return to near baseline levels. Given the potential importance of FSH in prostate cancer biology, the differential role of GnRH antagonists with LHRH agonists is worthy of further study.

Other studies have evaluated the use of GnRH antagonist in other clinical stages of prostate cancer as well as other hormonally mediated disorders. Preliminary evaluations suggest that prostate gland volume

reduction can be rapidly effected by GnRH antagonist. There may be more rapid resolution of pain associated with endometriosis following administration of GnRH antagonists. Earlier anecdotal studies using daily administration of cetrorelix had demonstrated rapid resolution of painful symptoms associated with advanced metastatic prostate cancer. Studies of larger patient populations have now shown that abarelix, administered on a Day 1, 15, 29, 57 and very 28 days thereafter can induce meaningful remissions in patients with advanced, symptomatic prostate cancer in whom LHRH agonists are relatively or absolutely contraindicated. Thus, the availability of GnRH antagonists have come full circle. Future studies will undoubtedly fully evaluate the potential of GnRH antagonists in a multitude of medical conditions which are exacerbated or induced by androgens and estrogens.

Pracis Pharmaceuticals, Inc., Cambridge MA, USA.

## Abarelix: Clinical Benefits in Prostate Cancer

### Schulman C

Whereas GnRH agonists initially stimulate GnRH receptors, abarelix as a pure GnRH antagonist directly blocks the GnRH receptors. A phase II study in prostate cancer showed that abarelix depot causes faster decreases in testosterone (T) and other gonadal hormones compared with a GnRH agonist (alone or maximum androgen blockade MAB) as prospective, non-randomised, concurrent control. This was further evaluated in 3 multicentre, randomised phase III studies comparing abarelix depot 100 mg with a GnRH agonist (leuprolide 7.5 mg or goserelin 3.6 mg) alone by 4-weekly injection or as MAB with bicalutamide 50 mg. Almost 700 patients were enrolled. Abarelix depot was superior to the GnRH agonist alone or as MAB in avoiding initial testosterone surge (T not  $\geq 10\%$  of baseline) and achieving faster castration (T  $\leq 50$  ng/mL: within 1 week versus  $\geq 3$  weeks). Whereas 0% of patients receiving abarelix had a T surge, this occurred in 82–96% of patients receiving a GnRH agonist. After 1 week, castration was obtained in 56–72% of abarelix patients versus 0–1% of GnRH agonist patients. After 12 weeks castration was maintained in  $> 90\%$  of patients with all treatments. Abarelix depot also produced faster suppression of LH, FSH and DHT. The PSA decline was faster compared with the GnRH agonist. All treatments were well tolerated. Abarelix depot 100 mg in monotherapy induces faster reductions in T and other gonadal hormones than a GnRH agonist (in monotherapy or as MAB). PSA decline is faster compared with a GnRH agonist.

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## Pharmacological and Biochemical Properties of Abarelix, a Pure GnRH Antagonist

Karbon W,<sup>1</sup> Kennedy J,<sup>1</sup> Lafayette A,<sup>1</sup> Padagas J,<sup>1</sup> Wright C,<sup>1</sup> McGarr R,<sup>2</sup> Andresen J<sup>1</sup>

Abarelix is the first synthetic GnRH receptor antagonist that has been formulated as a one month

depot (abarelix depot), and is currently in clinical trials for the treatment of hormone-sensitive prostate cancer and endometriosis. In the present study, we characterized the pharmacological properties of abarelix (acetate salt) at the rat pituitary GnRH receptor and determined whether abarelix liberates histamine from isolated mast cells. In addition, we tested the ability of abarelix to regulate serum testosterone levels following acute administration.

[<sup>125</sup>I]-abarelix binding to GnRH receptors was studied in rat pituitary membranes. At 4 °C, the binding of [<sup>125</sup>I]-abarelix was saturable and achieved equilibrium, with an equilibrium dissociation constant (K<sub>D</sub>) calculated to be 0.1 nM. Unlabeled abarelix potently inhibited the binding of the LHRH agonist radioligand [<sup>125</sup>I]-des-Gly,<sup>10</sup>, D-Ala<sup>6</sup>-LHRH. The LHRH agonist, triptorelin, potently inhibited the binding of both radioligands.

In isolated rat peritoneal mast cells, exposure to low micromolar concentrations of the GnRH antagonist, Ac-D-p-Cl-Phe<sup>1,2</sup>, D-Trp<sup>3</sup>, D-Arg<sup>6</sup>, D-Ala<sup>10</sup>-GnRH, caused complete release, of cellular histamine. In contrast, abarelix did not produce a significant release of histamine at concentrations up to 0.3 mM, demonstrating that it has low histamine releasing potential. Acute administration of abarelix dose-dependently and reversibly lowered serum testosterone levels in rats.

These findings demonstrate the unique mechanism of action of a GnRH antagonist and suggest potential clinical roles for abarelix depot in disease states where rapidity of action and avoidance of hormonal surge are desirable.

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<sup>2</sup>Praecis Pharmaceuticals Inc., Cambridge, MA, USA.

## Phase I/II Clinical Study of a Novel GnRH Analogue

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**Background:** GnRHI is a chemically conjugated analogue of GnRH, administered by subcutaneous injection. Pre-clinical studies show that GnRHI induces antibodies to native GnRH. The effects in the male are analogous to castration. **Objective:** To investigate the local and systemic tolerability of an immunisation regimen in patients with metastatic prostate gland cancer. **Methods:** An open evaluation of an increasing (5 microg to 80 microg GnRHI peptide content) regimen administered at 0, 3 and 6 weeks. Fifty-three patients received treatment. Safety and efficacy were assessed over the 12-weeks following first administration. **Results:** No systemic allergic reactions were observed. Tolerable, minor, short-term injection site reactions were observed. Adverse events, study withdrawals and some expected abnormal clinical laboratory results were observed, but were related to the patients' underlying condition or to the use of flutamide. The most consistent abnormal and significant result related to raised liver function tests, considered related to use of flutamide. GnRHI had no clinically significant effect on heart rate, blood pressure, pain score, performance status or clinical status, and no adverse event was directly attributable to its use. Consistent production of GnRH antibodies was not observed. **Conclusions:** The therapy was well tolerated, with safety demonstrated to the 3 x 80 microg dose level. Studies are proceeding using an alternative formulation to enable the administration of higher doses of peptide.

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### FIRST TURKISH & UNITED STATES FORENSIC SCIENCES MEETING SEPTEMBER 9-13, 2002 ISTANBUL TURKEY

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